

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Lercanidipine Clonmel 10 mg and 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lercanidipine Clonmel 10 mg Film-Coated Tablets.

One tablet contains 10 mg of lercanidipine hydrochloride as lercanidipine hydrochloride hemihydrate. This is equivalent to 9.4 mg of lercanidipine.

Each film-coated tablet contains 36.55 mg lactose-monohydrate.

Lercanidipine Clonmel 20 mg Film-Coated Tablets.

One tablet contains 20 mg of lercanidipine hydrochloride as lercanidipine hydrochloride hemihydrate. This is equivalent to 18.8 mg of lercanidipine.

Each film-coated tablet contains 73.1 mg lactose-monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Lercanidipine Clonmel 10 mg Film-Coated Tablets.

Yellow, round, biconvex film-coated tablets with breaking notch.

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

Lercanidipine Clonmel 20 mg Film-Coated Tablets.

Pink, round, biconvex film-coated tablets with breaking notch. The tablets can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Method of administration:

Oral use

The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). The recommended dosage is 10 mg once a day at least 15 minutes before meals (preferably before breakfast); 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- 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 side effects may increase.

Use in the 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.

Use in children

Lercanidipine is not recommended for use in children below the age of 18 years due to insufficient data on safety and efficacy.

Use in patients with 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 (GFR <30 ml/min).

4.3 Contraindications

- Hypersensitivity to the active substance lercanidipine hydrochloride, to any dihydropyridine or to any of the excipients
- Pregnancy and lactation (see 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 4.5)
 - ciclosporin (see 4.5)
 - grapefruit juice (see 4.5).

4.4 Special warnings and precautions for use

Special care should be exercised when lercanidipine is used in patients with sick sinus syndrome (if a pacemaker is not *in situ*). Although haemodynamic 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 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 4.8).

Use in patients with 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 (GFR <30 ml/min) (see 4.2).

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

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 4.5).

Lercanidipine Clonmel 10 mg Tablets

1 tablet contains 36.55 mg lactose monohydrate and therefore should not be administered to patients with Lapp lactase insufficiency, galactosaemia or glucose/galactose malabsorption syndrome.

Lercanidipine Clonmel 20 mg Tablets

1 tablet contains 73.1 mg 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 interaction

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 lercanidipine with inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir, erythromycin, troleanomycin) should be avoided (see 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 and lercanidipine should not be administered together (see 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.

Lercanidipine should not be taken with grapefruit juice (see 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.

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.

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

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.

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 medicines of this class. Consequently, lercanidipine may be safely administered with β -blockers, but dose adjustment may be required.

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

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.

Co-administration of 20 mg lercanidipine in patients chronically treated with b-methyl digoxin 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.

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.

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

Lercanidipine has been safely administered with diuretics and ACE inhibitors.

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

4.6 Pregnancy and lactation

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, lercanidipine should not be administered during pregnancy or to women with child-bearing potential unless effective contraception is used. 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

Clinical experience with lercanidipine indicates that it is unlikely to impair a patient's ability to drive or use machinery. However, caution should be exercised because dizziness, asthenia, fatigue and rarely somnolence may occur.

4.8 Undesirable effects

In this section frequencies of undesirable effects are defined as follows: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

About 1.8% of treated patients experienced adverse reactions.

The list below shows the incidence of adverse drug reactions, at least possibly causally related, grouped by MedDRA system organ class, and ranked by frequency (uncommon, rare).

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.

Investigations

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

Cardiac disorders

Uncommon: Tachycardia; palpitations.

Rare: Angina pectoris.

Some dihydropyridines may lead to precordial pain or angina pectoris.

Very rare: Patients with pre-existing angina pectoris may experience increased frequency, duration or severity of these attacks. Isolated cases of myocardial infarction may be observed.

Nervous system disorders

Uncommon: Headache; dizziness.

Rare: Somnolence.

Gastrointestinal disorders

Rare: Nausea; dyspepsia; diarrhoea; abdominal pain; vomiting.

Renal and urinary disorders

Rare: Polyuria.

Skin and subcutaneous tissue disorders

Rare: Rash.

Musculoskeletal and connective tissue disorders

Rare: Myalgia.

Vascular disorders

Uncommon: Flushing.

Very rare: Syncope

General disorders and administration site conditions

Uncommon: Oedema peripheral.

Rare: Asthenia; fatigue.

In post-marketing experience from spontaneous reports, the following undesirable effects were reported:

Investigations

Very rare: Reversible increases in serum levels of hepatic transaminases.

Gastrointestinal disorders

Very rare: Gingival hypertrophy.

Renal and urinary disorders

Very rare: Urinary frequency.

Vascular disorders

Very rare: Hypotension.

General disorders and administration site conditions

Very rare: Chest pain.

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). The first patient

developed sleepiness and was treated by gastric lavage. The second patient developed cardiogenic shock with severe myocardial ischaemia and mild renal failure and was treated with high-dose catecholamines, furosemide, digitalis and parenteral plasma expanders. The third patient developed vomiting and hypotension and was treated with active charcoal, laxative and dopamine infusion. All three cases resolved without sequelae.

Overdose 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 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
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 \pm 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 \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 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 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.

Characteristics in patients

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

Lactose monohydrate
Pregelatinised maize starch
Croscarmellose sodium
Hypromellose
Silica, colloidal anhydrous
Magnesium stearate

Film

Opadry yellow (10 mg tablet)

Hypromellose
Macrogol 8000
Titanium dioxide (E171)
Talc
Iron oxide yellow (E172)

Opadry pink (20 mg tablet):

Hypromellose
Macrogol 8000
Titanium dioxide (E171)
Talc
Iron oxide red (E172) – 20 mg tablet

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

Lercanidipine Clonmel 20 mg tablets: The tablet halves should be stored protected from light.

6.5 Nature and contents of container

White-opaque Aluminium/PVC/PVdC blisters.

Pack sizes: 10, 14, 28, 30, 50, 56, 84, 98, 100, 126 or 154 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary
Ireland

8. MARKETING AUTHORISATION NUMBER

Lercanidipine Clonmel 10 mg tablets: PA 126/187/1
Lercanidipine Clonmel 20 mg tablets: PA 126/187/2

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th March 2010.

10. DATE OF REVISION OF THE TEXT

March 2011