Lercanidipine Hydrochloride 10mg and 20mg Film-Coated Tablets

PL 24668/0173-6

UKPAR

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Lercanidipine Hydrochloride 10mg and 20mg Film-Coated Tablets

PL 24668/0173-6

LAY SUMMARY

On 22\textsuperscript{nd} December 2009, the MHRA granted Caduceus Pharma Limited Marketing Authorisations (licences) for Lercanidipine Hydrochloride 10mg and 20mg Film-Coated Tablets (PL 24668/0173-6).

This medicine is used to treat mild to moderate high blood pressure, also known as hypertension.

This medicine contains lercanidipine hydrochloride. Lercanidipine belongs to a group of medicines called calcium channel blockers. These work by blocking the entry of calcium into the muscle cells of the heart and the blood vessels that carry blood away from the heart.

It is the entry of calcium into these cells that causes the heart to contract and blood vessels to narrow. By blocking the entry of calcium, calcium channel blockers decrease contraction of the heart and widen the blood vessels, and the blood pressure is reduced.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Lercanidipine Hydrochloride 10mg and 20mg Film-Coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.
Lercanidipine Hydrochloride 10mg and 20mg Film-Coated Tablets

PL 24668/0173-6

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted Caduceus Pharma Limited Marketing Authorisations for the medicinal products Lercanidipine Hydrochloride 10mg and 20mg Film-Coated Tablets (PL 24668/0173-6) on 22nd December 2009. The products are prescription only medicines (POM) indicated in adults (over 18 years of age) for the treatment of mild to moderate essential hypertension.

These applications for Lercanidipine Hydrochloride 10mg and 20mg Film-Coated Tablets are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Zanidip 10mg and 20mg Tablets, first authorised in the UK to Recordati Industria Chimica e Farmaceutica S.p.A. in March 1996.

There are two duplicate applications for Lercanidipine 10mg and 20mg Film-Coated Tablets which have been approved. The information for both sets of licences are identical.

The product contains lercanidipine which is a selective calcium channel blocker (with mainly vascular effects).

Lercanidipine hydrochloride is a third generation dihydropyridine calcium antagonist. Lercanidipine exists as a racemate, with anti-hypertensive activity residing primarily in the S-enantiomer. The R-enantiomer and S-enantiomers show similar plasma profiles. No interconversion of the enantiomers occurs in vivo.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Lercanidipine hydrochloride
INN: Lercanidipine hydrochloride
Chemical name: 1,4 - Dihydro - 2,6 - dimethyl - 4 - (3 -nitrophenyl) - 3,5 — pyridinedicarboxylic acid - 2 -[(3,3 - diphenylpropyl) methylamino] — 1,1 - dimethylethyl methyl ester hydrochloride

Structure:

![Structure diagram]

Physical form: A yellow powder (crystalline form).
Solubility: Soluble in methanol and practically insoluble in water.

Molecular formula: C_{36}H_{41}N_{3}O_{6} . HCl
Molecular weight: 648.19

Lercanidipine hydrochloride complies with in-house specifications.

A Drug Master File (DMF) has been provided covering the manufacture and control of the drug substance lercanidipine hydrochloride.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the drug substance.

An appropriate specification is provided for lercanidipine hydrochloride, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications.

Satisfactory specifications and certificates of analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Suitable certificates of analysis have been provided for all reference standards used.
Appropriate stability data have been generated showing lercanidipine hydrochloride to be physically and chemically stable drugs, and supporting an appropriate retest period.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients inside the tablet core are pharmaceutical excipients magnesium stearate, povidone, sodium starch glycolate (Type A), lactose monohydrate and microcrystalline cellulose.

The tablet film-coating consists of pharmaceutical excipients macrogol, polyvinyl alcohol, talc, titanium dioxide (E 171) and yellow iron oxide (E 172).

For the film-coating of the 20mg Film-Coated Tablets there is an additional excipient of red iron oxide (E 172).

All of the excipients with the exception of the excipients in the tablet film-coating comply with their relevant European Pharmacopoeia monographs. The tablet film-coating excipients comply with in-house specifications.

None of the excipients used contain material of animal or human origin. The magnesium stearate contained in this product is sourced from vegetable origin and therefore no European Pharmacopoeia Certificates of suitability for TSE is required.

The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these products.

**Product development**

The objective of the development programme was to produce products that could be considered generic medicinal products of Zanidip 10mg and 20mg Tablets (Recordati Industria Chimica e Farmaceutica S.p.A.).

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative dissolution and impurity profiles have been provided for the finished product versus the reference products.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on pilot scale batches of finished product and the results appear satisfactory. The applicant has committed to perform process validation on future commercial-scale batches.

**Finished product specification**

The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply
with the release specifications. Certificates of analysis for all working standards used have been provided and are satisfactory.

**Container-Closure System**
The product is packaged in two types of blister packs consisting of polyvinylchloride and aluminium, and polyvinylidene chloride and aluminium, both with push-through foil. The product comes in pack sizes of 7, 10, 14, 20, 28, 30, 35, 50, 56, 60, 98 and 100 film-coated tablets. The 20mg dose product has the extra pack size of 42 film-coated tablets.

Specifications and certificates of analysis have been provided. All primary product packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf life of 2 years has been set, with storage conditions ‘Do not store above 25°C’ and ‘Store in the original package in order to protect from moisture’. This is satisfactory.

**ADMINISTRATIVE**
**Expert Report**
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

**Summary of Product Characteristics (SPC)**
These are pharmaceutically satisfactory.

**Labelling**
These are pharmaceutically satisfactory.

**Patient Information Leaflet (PIL)**
This is pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA Form**
These are pharmaceutically satisfactory.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

These applications for Lercanidipine Hydrochloride 10mg and 20mg Film-Coated Tablets are submitted as abridged standard applications according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal products of Zanidip 10mg and 20mg Tablets, first authorised in the UK to Recordati Industria Chimica e Farmaceutica S.p.A. in March 1996.

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
To support the applications, the marketing authorisation holder has included a single bioequivalence study:

An open-label, randomized, 2-treatment, 4-period, 2 sequence, single dose, crossover bioequivalence study comparing the pharmacokinetics of Lercanidipine Hydrochloride 20mg Film-Coated Tablets (Test) versus Corifeo 20mg Tablets (Reference) under fasted conditions.

Corifeo 20 mg Tablets licensed in Germany were used as the reference product in the bioequivalence study. This is considered to be equivalent to the UK reference product, Zanidip 20 mg Tablets.

Blood sampling was performed pre-drug administration, during the study and up to 48 hours post dose in each treatment period. There was a washout period of 7 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-t} (\text{pg/ml/h})$</th>
<th>$\text{AUC}_{0-\infty} (\text{pg/ml/h})$</th>
<th>$\text{C}_{\text{max}} (\text{pg/ml})$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S-Lercanidipine:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test (1&lt;sup&gt;st&lt;/sup&gt; administration)</td>
<td>24773.64</td>
<td>25779.04</td>
<td>5396.34</td>
</tr>
<tr>
<td>Test (2&lt;sup&gt;nd&lt;/sup&gt; administration)</td>
<td>35554.92</td>
<td>37273.53</td>
<td>8128.96</td>
</tr>
<tr>
<td>Reference (1&lt;sup&gt;st&lt;/sup&gt; administration)</td>
<td>28512.33</td>
<td>29470.77</td>
<td>5885.96</td>
</tr>
<tr>
<td>Reference (2&lt;sup&gt;nd&lt;/sup&gt; administration)</td>
<td>34096.52</td>
<td>35625.31</td>
<td>7043.96</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>0.94 (0.86 – 1.04)</td>
<td>0.95 (0.86 – 1.05)</td>
<td>1.02 (0.89 – 1.16)</td>
</tr>
<tr>
<td><strong>R-Lercanidipine:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test (1&lt;sup&gt;st&lt;/sup&gt; administration)</td>
<td>26453.99</td>
<td>27683.67</td>
<td>5313.90</td>
</tr>
<tr>
<td>Test (2&lt;sup&gt;nd&lt;/sup&gt; administration)</td>
<td>37137.92</td>
<td>39476.96</td>
<td>7896.60</td>
</tr>
<tr>
<td>Reference (1&lt;sup&gt;st&lt;/sup&gt; administration)</td>
<td>29533.13</td>
<td>31229.65</td>
<td>5669.19</td>
</tr>
<tr>
<td>Reference (2&lt;sup&gt;nd&lt;/sup&gt; administration)</td>
<td>35151.10</td>
<td>37087.59</td>
<td>6771.79</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>0.97 (0.87 – 1.08)</td>
<td>0.97 (0.87 – 1.07)</td>
<td>1.07 (0.90 – 1.18)</td>
</tr>
</tbody>
</table>

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for $\text{AUC}_{0-t}$ and $\text{C}_{\text{max}}$ for both enantiomers S- and R- lercanidipine lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.
EFFICACY
No new data has been provided.

SAFETY
No new data has been provided.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORMS (MAA)
These are satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
These are consistent with those for the reference products and are satisfactory.

DISCUSSION
The applicant has satisfactorily demonstrated bioequivalence between the test and reference products.

MEDICAL CONCLUSION
The bioequivalence study submitted has shown that Lercanidipine Hydrochloride 10mg and 20mg Film-Coated Tablets can be considered as generic medicinal products to the originator products Zanidip 10mg and 20mg Tablets (Recordati Industria Chimica e Farmaceutica S.p.A.).

The grant of marketing authorisations is recommended for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Lercanidipine Hydrochloride 10mg and 20mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Lercanidipine Hydrochloride 20mg Film-Coated Tablets and the reference product. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the Lercanidipine Hydrochloride 20mg Film-Coated Tablets can be extrapolated to Lercanidipine Hydrochloride 10mg Film-Coated Tablets

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with lercanidipine is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
Lercanidipine Hydrochloride 10mg and 20mg Film-Coated Tablets

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**STEPS TAKEN FOR ASSESSMENT**

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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 26\textsuperscript{th} February 2008.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 13\textsuperscript{th} March 2008.</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications, the MHRA requested further information on the clinical sections of the dossier on 4\textsuperscript{th} August 2008 and 31\textsuperscript{st} March 2009.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the clinical sections of the dossier on 27\textsuperscript{th} January 2009 and 23\textsuperscript{rd} June 2009.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 22\textsuperscript{nd} December 2009.</td>
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Lercanidipine Hydrochloride 10mg and 20mg Film-Coated Tablets

PL 24668/0173-6

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Lercanidipine Hydrochloride 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One film-coated tablet contains 10 mg lercanidipine hydrochloride, equivalent to 9.4 mg lercanidipine. Excipient: Lercanidipine Hydrochloride 10 mg film-coated tablets: Lactose monohydrate 30 mg For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablets
Lercanidipine Hydrochloride 10 mg film-coated tablets: Yellow, round, biconvex 6.5 mm film-coated tablets, 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
Lercanidipine is indicated for the treatment of mild to moderate essential hypertension.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
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 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.

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

Renal insufficiency
Special care should be exercised when treatment is commenced in patients with mild to moderate renal impairment. Although the usually recommended dose schedule may be tolerated, an increase in dose to 20mg daily must be approached with caution. Lercanidipine is not recommended for use in patients with severe renal impairment (GFR < 30 ml/min).

Hepatic insufficiency
Special care should be exercised when treatment is commenced in patients with mild to moderate hepatic dysfunction. Although the usually recommended dose schedule may be tolerated, 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.

Administration
The tablets should be taken with some water before a meal.

4.3 CONTRAINDICATIONS
- Hypersensitivity to lercanidipine, to any dihydropyridine or to any of the excipients.
- Left ventricular outflow tract obstruction.
- Untreated congestive cardiac failure.
- Unstable angina pectoris.
- Within 1 month of a myocardial infarction.
- Severe renal or hepatic impairment.
- Pregnancy and lactation (see section 4.6).
- Women of child-bearing potential unless effective contraception is used.
- Strong inhibitors of CYP3A4 (see section 4.5).
- Cyclosporin (see section 4.5).
- 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 (if a pacemaker is not in situ). Although hemodynamic controlled studies revealed no impairment of ventricular function, care is also required in patients with LV dysfunction. It has been suggested that some short-acting dihydropyridines may be associated with increased cardiovascular risk in patients with ischaemic heart disease. Although 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 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 (GFR < 30 ml/min) (see 4.2).

Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive drugs (see 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 INTERACTION

**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 (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 Cmax 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<sub>max</sub> 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), 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**
Healthy volunteers treated with digoxin following dosing with 20 mg lercanidipine given fasted showed a mean increase of 33% in digoxin C<sub>max</sub>, while AUC and renal clearance were not significantly modified. Patients on concomitant digoxin treatment should be closely monitored clinically for signs of digoxin toxicity.
Co-administration of 20 mg lercanidipine in patients chronically treated with b-methyldigoxin showed no evidence of pharmacokinetic interaction.

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 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.
Lactation
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
Lercanidipine 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: \(\geq 1/10\)
Common: \(\geq 1/100, < 1/10\)
Uncommon: \(\geq 1/1,000, < 1/100\)
Rare: \(\geq 1/10,000, < 1/1,000\)
Very rare: \(< 1/10,000\), cannot be estimated from the available data

Investigations
Very rare: reversible increases in serum levels of hepatic transaminases

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.

Nervous system disorders
Uncommon: headache; dizziness

Gastrointestinal disorders
Rare: nausea; dyspepsia; diarrhoea; abdominal pain; vomiting
Very rare: gingival hypertrophy

Renal and urinary disorders
Rare: polyuria
Very rare: urinary frequency

Skin and subcutaneous tissue disorders
Rare: rash

Musculoskeletal and connective tissue disorders
Rare: myalgia

Vascular disorders
Uncommon: flushing

General disorders and administration site conditions
Rare: asthenia; fatigue

Immune system disorders
Very rare: hypersensitivity

Psychiatric disorders
Rare: somnolence

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

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).
As with other dihydropyridines, 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 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 ± 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.

**Metabolism**

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
- Talc
- Titanium dioxide (E 171)
- Yellow iron oxide (E 172)

**6.2 INCOMPATIBILITIES**

Not applicable.

**6.3 SHELF LIFE**

2 years

**6.4 SPECIAL PRECAUTIONS FOR STORAGE**

AI/PVC blister:
- Do not store above 25°C. Store in the original package in order to protect from moisture.

AI/PVDC blister:
- Do not store above 25°C. Store in the original package in order to protect from moisture.

**6.5 NATURE AND CONTENTS OF CONTAINER**

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

*Pack sizes: 7, 10, 14, 20, 28, 30, 35, 50, 56, 60, 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**

Cadleceus Pharma Ltd
- 6th Floor
- 94 Wigmore Street
- London
- W1U 3RF
- UK

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 24668/0173

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

22/12/2009

**10 DATE OF REVISION OF THE TEXT**

22/12/2009
1 NAME OF THE MEDICINAL PRODUCT
Lercanidipine Hydrochloride 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:
Lercanidipine Hydrochloride 20 mg film-coated tablets: Lactose monohydrate 60 mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablets
Lercanidipine Hydrochloride 20 mg film-coated tablets: Pink, round, biconvex 8.5 mm film-coated tablets, 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
Lercanidipine is indicated for the treatment of mild to moderate essential hypertension.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
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 to therapy with a beta-adrenoceptor 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.

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

Renal insufficiency
Special care should be exercised when treatment is commenced in patients with mild to moderate renal impairment. Although the usually recommended dose schedule may be tolerated, an increase in dose to 20mg daily must be approached with caution.
Lercanidipine is not recommended for use in patients with severe renal impairment (GFR < 30 ml/min).

Hepatic insufficiency
Special care should be exercised when treatment is commenced in patients with mild to moderate hepatic dysfunction. Although the usually recommended dose schedule may be tolerated, 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.

Administration
The tablets should be taken with some water before a meal.

4.3 CONTRAINDICATIONS
- Hypersensitivity to lercanidipine, to any dihydropyridine or to any of the excipients.
- Left ventricular outflow tract obstruction.
- Untreated congestive cardiac failure.
- Unstable angina pectoris.
- Within 1 month of a myocardial infarction.
- Severe renal or hepatic impairment.
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 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.

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 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 (GFR < 30 ml/min) (see 4.2).
Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive drugs (see 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 INTERACTION

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 (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 Cmax 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 \( t_{\text{max}} \) 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), 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**
Healthy volunteers treated with digoxin following dosing with 20 mg lercanidipine given fasted showed a mean increase of 33% in digoxin \( C_{\text{max}} \), while AUC and renal clearance were not significantly modified. Patients on concomitant digoxin treatment should be closely monitored clinically for signs of digoxin toxicity.

Co-administration of 20 mg lercanidipine in patients chronically treated with \( \beta \)-methyldigoxin showed no evidence of pharmacokinetic interaction.

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, \( \beta \)-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 \( \beta \)-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 \( \beta \)-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 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.

**Lactation**
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
Lercanidipine 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, < 1/10
Uncommon: ≥ 1/1,000, < 1/100
Rare: ≥ 1/10,000, < 1/1,000
Very rare: < 1/10,000, cannot be estimated from the available data

Investigations
Very rare: reversible increases in serum levels of hepatic transaminases

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.

Nervous system disorders
Uncommon: headache; dizziness

Gastrointestinal disorders
Rare: nausea; dyspepsia; diarrhoea; abdominal pain; vomiting
Very rare: gingival hypertrophy

Renal and urinary disorders
Rare: polyuria
Very rare: urinary frequency

Skin and subcutaneous tissue disorders
Rare: rash

Musculoskeletal and connective tissue disorders
Rare: myalgia

Vascular disorders
Uncommon: flushing

General disorders and administration site conditions
Rare: asthenia; fatigue

Immune system disorders
Very rare: hypersensitivity

Psychiatric disorders
Rare: somnolence

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

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).

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Signs/Symptoms</th>
<th>Management</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg</td>
<td>Sleepiness</td>
<td>Gastric lavage</td>
<td>Recovered</td>
</tr>
<tr>
<td>undefined</td>
<td></td>
<td>Active charcoal</td>
<td></td>
</tr>
</tbody>
</table>
As with other dihydropyridines, 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 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.

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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.

**Metabolism**
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.

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**Elderly, renal and hepatic insufficiency**
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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
- Talc
- 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
Al/PVC blister:
- Do not store above 25°C. Store in the original package in order to protect from moisture.
Al/PVDC blister:
- Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER
Blister pack (Aluminium/PVC) with push-through foil.
Blister pack (Aluminium/PVDC) with push-through foil.

Pack sizes: 7, 10, 14, 20, 28, 30, 35, 42, 50, 56, 60, 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
Caduceus Pharma Ltd
6th Floor
94 Wigmore Street
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0174

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/12/2009

10 DATE OF REVISION OF THE TEXT
22/12/2009
1 NAME OF THE MEDICINAL PRODUCT
Lercanidipine Hydrochloride 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One film-coated tablet contains 10 mg lercanidipine hydrochloride, equivalent to 9.4 mg lercanidipine.
Excipient:
Lercanidipine Hydrochloride 10 mg film-coated tablets: Lactose monohydrate 30 mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablets
Lercanidipine Hydrochloride 10 mg film-coated tablets: Yellow, round, biconvex 6.5 mm film-coated tablets, 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
Lercanidipine is indicated for the treatment of mild to moderate essential hypertension.

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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 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.

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

Renal insufficiency
Special care should be exercised when treatment is commenced in patients with mild to moderate renal impairment. Although the usually recommended dose schedule may be tolerated, an increase in dose to 20mg daily must be approached with caution.
Lercanidipine is not recommended for use in patients with severe renal impairment (GFR < 30 ml/min).

Hepatic insufficiency
Special care should be exercised when treatment is commenced in patients with mild to moderate hepatic dysfunction. Although the usually recommended dose schedule may be tolerated, 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.

Administration
The tablets should be taken with some water before a meal.

4.3 CONTRAINDICATIONS
- Hypersensitivity to lercanidipine, to any dihydropyridine or to any of the excipients.
- Left ventricular outflow tract obstruction.
- Untreated congestive cardiac failure.
- Unstable angina pectoris.
- Within 1 month of a myocardial infarction.
- Severe renal or hepatic impairment.
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 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.

**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 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 (GFR < 30 ml/min) (see 4.2).

Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive drugs (see 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 INTERACTION

**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 (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).

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 ($t_{\text{max}}$ 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), 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**

Healthy volunteers treated with digoxin following dosing with 20 mg lercanidipine given fasted showed a mean increase of 33% in digoxin $C_{\text{max}}$, while AUC and renal clearance were not significantly modified. Patients on concomitant digoxin treatment should be closely monitored clinically for signs of digoxin toxicity.

Co-administration of 20 mg lercanidipine in patients chronically treated with b-methyldigoxin showed no evidence of pharmacokinetic interaction.

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 hypertensive 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 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.

**Lactation**

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
Lercanidipine 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: \( \geq 1/10 \)
Common: \( \geq 1/100, < 1/10 \)
Uncommon: \( \geq 1/1,000, < 1/100 \)
Rare: \( \geq 1/10,000, < 1/1,000 \)
Very rare: \( < 1/10,000 \), cannot be estimated from the available data

Investigations
Very rare: reversible increases in serum levels of hepatic transaminases

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.

Nervous system disorders
Uncommon: headache; dizziness

Gastrointestinal disorders
Rare: nausea; dyspepsia; diarrhoea; abdominal pain; vomiting
Very rare: gingival hypertrophy

Renal and urinary disorders
Rare: polyuria
Very rare: urinary frequency

Skin and subcutaneous tissue disorders
Rare: rash

Musculoskeletal and connective tissue disorders
Rare: myalgia

Vascular disorders
Uncommon: flushing

General disorders and administration site conditions
Rare: asthenia; fatigue

Immune system disorders
Very rare: hypersensitivity

Psychiatric disorders
Rare: somnolence

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

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).

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Signs/Symptoms</th>
<th>Management</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg</td>
<td>Sleepiness</td>
<td>Gastric lavage</td>
<td>Recovered</td>
</tr>
<tr>
<td>+ undefined</td>
<td></td>
<td>Active charcoal</td>
<td></td>
</tr>
</tbody>
</table>
As with other dihydropyridines, 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 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 ± 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.

**Metabolism**
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
Talc
Titanium dioxide (E 171)
Yellow iron oxide (E 172)

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Al/PVC blister:
Do not store above 25°C. Store in the original package in order to protect from moisture.
Al/PVDC blister:
Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER
Blister pack (Aluminium/PVC) with push-through foil.
Blister pack (Aluminium/PVDC) with push-through foil.

Pack sizes: 7, 10, 14, 20, 28, 30, 35, 50, 56, 60, 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
Caduceus Pharma Ltd
6th Floor
94 Wigmore Street
London
W1U 3RF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0175

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/12/2009

10 DATE OF REVISION OF THE TEXT
22/12/2009
1 NAME OF THE MEDICINAL PRODUCT
Lercanidipine Hydrochloride 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:
Lercanidipine Hydrochloride 20 mg film-coated tablets: Lactose monohydrate 60 mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablets
Lercanidipine Hydrochloride 20 mg film-coated tablets: Pink, round, biconvex 8.5 mm film-coated tablets, 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
Lercanidipine is indicated for the treatment of mild to moderate essential hypertension.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
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 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.

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

Renal insufficiency
Special care should be exercised when treatment is commenced in patients with mild to moderate renal impairment. Although the usually recommended dose schedule may be tolerated, an increase in dose to 20mg daily must be approached with caution.
Lercanidipine is not recommended for use in patients with severe renal impairment (GFR < 30 ml/min).

Hepatic insufficiency
Special care should be exercised when treatment is commenced in patients with mild to moderate hepatic dysfunction. Although the usually recommended dose schedule may be tolerated, 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.

Administration
The tablets should be taken with some water before a meal.

4.3 CONTRAINDICATIONS
- Hypersensitivity to lercanidipine, to any dihydropyridine or to any of the excipients.
- Left ventricular outflow tract obstruction.
- Untreated congestive cardiac failure.
- Unstable angina pectoris.
- Within 1 month of a myocardial infarction.
- Severe renal or hepatic impairment.
- Pregnancy and lactation (see section 4.6).
- Women of child-bearing potential unless effective contraception is used.
- Strong inhibitors of CYP3A4 (see section 4.5).
- Cyclosporin (see section 4.5).
- 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 (if a pacemaker is not in situ). Although hemodynamic controlled studies revealed no impairment of ventricular function, care is also required in patients with LV dysfunction. It has been suggested that some short-acting dihydropyridines may be associated with increased cardiovascular risk in patients with ischaemic heart disease. Although 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 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 (GFR < 30 ml/min) (see 4.2).
Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive drugs (see 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.

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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 (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).

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 ($t_{\text{max}}$ was delayed from 1.75 to 3 hours). Midazolam concentrations were not modified.

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

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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 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.

**Lactation**
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**
Lercanidipine 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.

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

Assessment of frequencies:
- **Very common**: \( \geq 1/10 \)
- **Common**: \( \geq 1/100, < 1/10 \)
- **Uncommon**: \( \geq 1/1,000, < 1/100 \)
- **Rare**: \( \geq 1/10,000, < 1/1,000 \)
- **Very rare**: \(< 1/10,000, \text{cannot be estimated from the available data} \)

**Investigations**
- Very rare: reversible increases in serum levels of hepatic transaminases

**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.

**Nervous system disorders**
- Uncommon: headache; dizziness

**Gastrointestinal disorders**
- Rare: nausea; dyspepsia; diarrhoea; abdominal pain; vomiting
- Very rare: gingival hypertrophy

**Renal and urinary disorders**
- Rare: polyuria
- Very rare: urinary frequency

**Skin and subcutaneous tissue disorders**
- Rare: rash

**Musculoskeletal and connective tissue disorders**
- Rare: myalgia

**Vascular disorders**
- Uncommon: flushing

**General disorders and administration site conditions**
- Rare: asthenia; fatigue

**Immune system disorders**
- Very rare: hypersensitivity

**Psychiatric disorders**
- Rare: somnolence

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

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).

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As with other dihydropyridines, 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 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

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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.

**Metabolism**
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
Talc
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
Al/PVC blister:
Do not store above 25°C. Store in the original package in order to protect from moisture.
Al/PVDC blister:
Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER
Blister pack (Aluminium/PVC) with push-through foil.
Blister pack (Aluminium/PVDC) with push-through foil.

Pack sizes: 7, 10, 14, 20, 28, 30, 35, 42, 50, 56, 60, 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
Cadeceus Pharma Ltd
6th Floor
94 Wigmore Street
London
W1U 3RF
UK

8 MARKETING AUTHORIZATION NUMBER(S)
PL 24668/0176

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/12/2009

10 DATE OF REVISION OF THE TEXT
22/12/2009
PACKAGE LEAFLET: INFORMATION FOR THE USER

LERCANIDIPINE HYDROCHLORIDE 10MG FILM-COATED TABLETS
LERCANIDIPINE HYDROCHLORIDE 20MG FILM-COATED TABLETS

lercanidipine hydrochloride

Read all of this leaflet carefully before you start using this medicine.
• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Lercanidipine Hydrochloride Film-coated Tablets are and what they are used for
2. Before you take Lercanidipine Hydrochloride Film-coated Tablets
3. How to take Lercanidipine Hydrochloride Film-coated Tablets
4. Possible side effects
5. How to store Lercanidipine Hydrochloride Film-coated Tablets
6. Further information

1. WHAT LERCANIDIPINE HYDROCHLORIDE FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

Lercanidipine belongs to a group of medicines called calcium channel blockers. They block the entry of calcium into the muscle cells of the heart and the blood vessels that carry blood away from the heart. It is the entry of calcium into these cells that causes the heart to contract and blood vessels to narrow. By blocking the entry of calcium, calcium channel blockers decrease contraction of the heart and widen the blood vessels, and the blood pressure is reduced.

Take special care with Lercanidipine Hydrochloride Film-coated Tablets
You should consult your doctor before taking Lercanidipine Hydrochloride Film-coated Tablets if you:
• suffer from angina, as taking lercanidipine may lead to chest pain or increased frequency of chest pain
• have sick sinus syndrome and don’t have a pacemaker
• have problems with your liver or kidney, or you are on dialysis

Using other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Lercanidipine Hydrochloride Film-coated Tablets with certain other medicines (see below), may alter the effect of these medicines or of lercanidipine.

It is especially important for your doctor to know if you are already being treated with any of the following medicines:
• phenytoin or carbamazepine (medicines for epilepsy)
• rifampicin (a medicine to treat tuberculosis)
• midazolam (a medicine that helps you sleep)
• cimetidine, more than 800mg (a medicine for ulcers, indigestion, or heartburn)
• digoxin (a medicine to treat a heart problem)
• terfenadine or astemizole (medicines for allergies)
• amiodarone or quinidine (medicines to treat a fast heart beat)
• metoprolol (a medicine to treat high blood
Lercanidipine has been prescribed to you for treatment of mild to moderate high blood pressure, also known as hypertension.

2. BEFORE YOU TAKE LERCANIDIPINE HYDROCHLORIDE FILM-COATED TABLETS

Do not take Lercanidipine Hydrochloride Film-coated Tablets if you:

- are allergic (hypersensitive) to lercanidipine or to any of the ingredients in Lercanidipine Hydrochloride Film-coated Tablets
- have had allergic reactions to medicines closely related to lercanidipine (such as amlodipine, nicardipine, felodipine, isradipine, nifedipine or lacidipine)
- are suffering from certain heart diseases:
  - uncontrolled heart failure
  - an obstruction to flow of blood from the heart
  - unstable angina (angina at rest or progressively increasing)
  - if you have had heart attack less than one month ago
- have severe liver or kidney problems
- are pregnant, if you wish to become pregnant or if you are a woman of child-bearing age and do not use any contraceptive method
- are breast-feeding
- are taking ciclosporin
- are taking antifungal medicines (such as ketoconazole or itraconazole)
- drink grapefruit juice
- are taking macrolide antibiotics (such as erythromycin or troleandomycin)
- are taking antivirals (such as ritonavir for HIV) and simvastatin (a medicine for high cholesterol value)

Taking Lercanidipine Hydrochloride Film-coated Tablets with food and drink

You must not eat grapefruit or drink grapefruit juice as this may increase the effect of lercanidipine.

Alcohol should be avoided while taking Lercanidipine Hydrochloride film-coated tablets as combining the tablets with alcohol can cause dizziness/fainting, tiredness or weakness. This is because the medicine may lower your blood pressure considerably together with alcohol.

Pregnancy and breast-feeding

Ask your doctor for advice before taking any medicine.

If you are taking lercanidipine and think that you may be pregnant, consult your doctor. Lercanidipine should not be used if you are pregnant, if you wish to become pregnant or if you are a woman of childbearing age and do not use any contraceptive method.

Lercanidipine Hydrochloride Film-coated Tablets should not be used if you are breast-feeding.

Driving and using machines

Lercanidipine Hydrochloride Film-coated Tablets have a negligible influence on the ability to drive or use machines. However, side effect such as dizziness, weakness, tiredness and rarely sleepiness may occur. You should be careful until you know how you react to Lercanidipine.
Important information about some of the ingredients of Lercanidipine Hydrochloride Film-coated Tablets
Lercanidipine Hydrochloride Film-coated Tablets contain lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE LERCANIDIPINE HYDROCHLORIDE FILM-COATED TABLETS
Always take Lercanidipine Hydrochloride Film-coated Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
The usual dose is one Lercanidipine Hydrochloride 10 mg film-coated tablet daily at the same time each day. This is preferably in the morning at least 15 minutes before breakfast, because a high fat meal significantly increases your blood levels of the medicine.

Your doctor may decide you to increase your dose to one Lercanidipine Hydrochloride 20 mg film-coated tablet daily, if needed.

The tablets should preferably be swallowed whole with 1/2 glass of water. The tablets can be divided into equal halves.

Lercanidipine is not recommended for use in children and adolescents below 18 years.

If you take more lercanidipine than you should
Immediately contact a doctor or the nearest hospital casualty department.
Exceeding the correct dosage may cause your blood pressure to become too low, and your heart to beat irregularly or faster. It may also lead to unconsciousness.

5. HOW TO STORE LERCANIDIPINE HYDROCHLORIDE FILM-COATED TABLETS
Keep out of the reach and sight of children.

Do not use Lercanidipine Hydrochloride Film-coated Tablets after the expiry date, which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Storage conditions:
Do not store above 25°C. Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Lercanidipine Hydrochloride Film-coated Tablets contain

- The active substance is lercanidipine hydrochloride. One 10mg film-coated tablet contains 10mg lercanidipine hydrochloride, equivalent to 9.4mg lercanidipine.
- One 20mg film-coated tablet contains 20mg lercanidipine hydrochloride, equivalent to 18.8mg lercanidipine.

The other ingredients are:
- Tablet core: Magnesium stearate, povidone, sodium starch glycolate (Type A), lactose monohydrate, microcrystalline cellulose.
- Film-coating: 10mg tablets: Macrogol, polyvinyl alcohol, talc, titanium dioxide (E 171), yellow iron oxide (E 172).
- Film-coating: 20mg tablets: Macrogol, polyvinyl alcohol, talc, titanium dioxide (E 171), yellow iron oxide (E 172), red iron oxide (E 172).

What Lercanidipine Hydrochloride Film-coated Tablets look like and contents of the pack
If you forget to take your Lercanidipine Hydrochloride Film-coated Tablets
If you forget to take a dose of Lercanidipine Hydrochloride Film-coated Tablets then take it as soon as you remember, unless it is nearly time for your next dose.
Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, lercanidipine can cause side effects, although not everybody gets them.

Uncommon (occur in less than 1 out of 100 users):
Headache, dizziness, faster heartbeats, awareness of the beating of the heart, flushing (temporary redness of the face and neck), ankle swelling.

Rare (occur in less than 1 out of 1000 users):
Sleepiness, weakness, tiredness, nausea, vomiting, diarrhoea, abdominal pain, indigestion, rash, muscle pain, passage of large amounts of urine, angina pectoris.

Very rare (occur in less than 1 out of 10,000 users):
Fainting, allergic reaction, swelling of gums, increase in liver enzyme values (seen in blood tests), fall in blood pressure which can cause dizziness, light-headedness or fainting, more frequent urination, chest pain and heart attack.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Lercanidipine Hydrochloride 10mg Film-coated Tablets are yellow, round, biconvex 6.5mm film-coated tablets, scored on one side, and marked 'L' on the other side.
Lercanidipine Hydrochloride 20mg Film-coated Tablets are pink, round, biconvex 8.5mm film-coated tablets, scored on one side, and 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.

Pack sizes:
Blister packs containing:
Lercanidipine Hydrochloride 10mg Film-coated Tablets: 7, 10, 14, 20, 28, 30, 35, 50, 56, 60, 98, 100 tablets
Lercanidipine Hydrochloride 20mg Film-coated Tablets: 7, 10, 14, 20, 28, 30, 35, 42, 50, 56, 60, 98, 100 tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Caduceus Pharma Limited, 6th Floor, 94 Wigmore Street, London, W1U 3RF, UK

Manufacturer
Actavis hf. Reykjavikurvegur 78, IS-220 Hafnarfjordur, Iceland
Or
Actavis Ltd, BLB016 Bulebel Industrial Estate, Zejtun ZTN 3000, Malta

This product is distributed by
Winthrop Pharmaceuticals, PO Box 611, Guildford, Surrey, GU1 4YS, UK

This leaflet was last revised in December 2009.

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1018215-01
Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Lercanidipine Hydrochloride Film-coated Tablets are and what they are used for
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3. How to take Lercanidipine Hydrochloride Film-coated Tablets
4. Possible side effects
5. How to store Lercanidipine Hydrochloride Film-coated Tablets
6. Further information

1. WHAT LERCANIDIPINE HYDROCHLORIDE FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

Lercanidipine belongs to a group of medicines called calcium channel blockers. They block the entry of calcium into the muscle cells of the heart and the blood vessels that carry blood away from the heart. It is the entry of calcium into these cells that causes the heart to contract and blood vessels to narrow. By blocking the entry of calcium, calcium channel blockers decrease contraction of the heart and widen the blood vessels, and the blood pressure is reduced.

- are taking antifungal medicines (such as ketoconazole or itraconazole)
- drink grapefruit juice
- are taking macrolide antibiotics (such as erythromycin or troleandomycin)
- are taking antivirals (such as ritonavir for HIV)

Take special care with Lercanidipine Hydrochloride Film-coated Tablets

You should consult your doctor before taking Lercanidipine Hydrochloride Film-coated Tablets if you:

- suffer from angina, as taking lercanidipine may lead to chest pain or increased frequency of chest pain
- have sick sinus syndrome and don't have a pacemaker
- have problems with your liver or kidney, or you are on dialysis

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Lercanidipine Hydrochloride Film-coated Tablets with certain other medicines (see below), may alter the effect of these medicines or of lercanidipine.

It is especially important for your doctor to know if you are already being treated with any of the following medicines:

- phenytoin or carbamazepine (medicines for epilepsy)
- rifampicin (a medicine to treat tuberculosis)
- midazolam (a medicine that helps you sleep)
- cimetidine, more than 800 mg (a medicine for ulcers, indigestion, or heartburn)
- digoxin (a medicine to treat a heart problem)
- terfenadine or astemizole (medicines for
Lercanidipine has been prescribed to you for treatment of mild to moderate high blood pressure, also known as hypertension.

2. BEFORE YOU TAKE LERCANIDIPINE HYDROCHLORIDE FILM-COATED TABLETS

Do not take Lercanidipine Hydrochloride Film-coated Tablets if you:
- are allergic (hypersensitive) to lercanidipine or to any of the ingredients in Lercanidipine Hydrochloride Film-coated Tablets
- have had allergic reactions to medicines closely related to lercanidipine (such as amlodipine, nicardipine, felodipine, isradipine, nifedipine or lacidipine)
- are suffering from certain heart diseases:
  - uncontrolled heart failure
  - an obstruction to flow of blood from the heart
  - unstable angina (angina at rest or progressively increasing)
  - if you have had heart attack less than one month ago
- have severe liver or kidney problems
- are pregnant, if you wish to become pregnant or if you are a woman of child-bearing age and do not use any contraceptive method
- are breast-feeding
- are taking ciclosporin

- amiodarone or quinidine (medicines to treat a fast heart beat)
- metoprolol (a medicine to treat high blood pressure)
- simvastatin (a medicine for high cholesterol value)

Taking Lercanidipine Hydrochloride Film-coated Tablets with food and drink
You must not eat grapefruit or drink grapefruit juice as this may increase the effect of lercanidipine.

Alcohol should be avoided while taking Lercanidipine Hydrochloride film-coated tablets as combining the tablets with alcohol can cause dizziness/fainting, tiredness or weakness. This is because the medicine may lower your blood pressure considerably together with alcohol.

Pregnancy and breast-feeding
Ask your doctor for advice before taking any medicine.
If you are taking lercanidipine and think that you may be pregnant, consult your doctor.
Lercanidipine should not be used if you are pregnant, if you wish to become pregnant or if you are a woman of childbearing age and do not use any contraceptive method.
Lercanidipine Hydrochloride Film-coated Tablets should not be used if you are breast-feeding.
Driving and using machines
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Lercanidipine Hydrochloride Film-coated Tablets contain lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

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The tablets should preferably be swallowed whole with 1/2 glass of water. The tablets can be divided into equal halves.

Lercanidipine is not recommended for use in children and adolescents below 18 years.

please tell your doctor or pharmacist.

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What Lercanidipine Hydrochloride Film-coated Tablets contain
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The other ingredients are:
Tablet core: Magnesium stearate, povidone, sodium starch glycolate (Type A), lactose monohydrate, microcrystalline cellulose.
Film-coating 10 mg tablets: Macrogol, polyvinyl alcohol, talc, titanium dioxide (E 171), yellow iron oxide (E 172).
If you take more lercanidipine than you should
Immediately contact a doctor or the nearest hospital casualty department.
Exceeding the correct dosage may cause your blood pressure to become too low, and your heart to beat irregularly or faster. It may also lead to unconsciousness.

If you forget to take your Lercanidipine Hydrochloride Film-coated Tablets
If you forget to take a dose of Lercanidipine Hydrochloride Film-coated Tablets then take it as soon as you remember, unless it is nearly time for your next dose.
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If you have any further questions on the use of this product, ask your doctor or pharmacist.

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Headache, dizziness, faster heartbeats, awareness of the beating of the heart, flushing (temporary redness of the face and neck), ankle swelling.

Rare (occur in less than 1 out of 1000 users):
Sleepiness, weakness, tiredness, nausea, vomiting, diarrhoea, abdominal pain, indigestion, rash, muscle pain, passage of large amounts of urine, angina pectoris.

Very rare (occur in less than 1 out of 10,000 users):
Fainting, allergic reaction, swelling of gums, increase in liver enzyme values (seen in blood tests), fall in blood pressure which can cause dizziness, light-headedness or fainting, more frequent urination, chest pain and heart attack.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet,
UKPAR Lercanidipine Hydrochloride 10mg and 20mg Film-Coated Tablets

PACKAGE LEAFLET: INFORMATION FOR THE USER

LERCANIDIPINE HYDROCHLORIDE 10 mg FILM-COATED TABLETS
LERCANIDIPINE HYDROCHLORIDE 20 mg FILM-COATED TABLETS
(lercanidipine hydrochloride)

Read all of this leaflet carefully before you start using this medicine.
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• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Lercanidipine Hydrochloride film-coated tablets are and what they are used for.
2. Before you take Lercanidipine Hydrochloride film-coated tablets.
3. How to take Lercanidipine Hydrochloride film-coated tablets.
4. Possible side effects.
5. How to store Lercanidipine Hydrochloride film-coated tablets.
6. Further information.

1. WHAT LERCANIDIPINE HYDROCHLORIDE FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

• are taking antifungal medicines (such as ketoconazole or itraconazole)
• are taking macrolide antibiotics (such as erythromycin or troleandomycin)
• are taking antivirals (such as ritonavir for HIV)

Take special care with Lercanidipine Hydrochloride film-coated tablets -
You should consult your doctor before taking Lercanidipine Hydrochloride film-coated tablets if you:
• suffer from angina, as taking lercanidipine may lead to chest pain or increased frequency of chest pain
• have sick sinus syndrome and don’t have a pacemaker
• have problems with your liver or kidney, or you are on dialysis.

Using other medicines - Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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It is especially important for your doctor to know if you are already being treated with any of the following medicines:
• phenytoin or carbamazepine (medicines for epilepsy)
• rifampicin (a medicine to treat tuberculosis)
• midazolam (a medicine that helps you sleep)
• cimetidine, more than 800 mg (a medicine for ulcers, indigestion, or heartburn)
• digoxin (a medicine to treat a heart problem)
• terfenadine or astemizole (medicines for allergies)
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Lercanidipine has been prescribed to you for treatment of mild to moderate high blood pressure, also known as hypertension.

2. BEFORE YOU TAKE LERCANIDIPINE HYDROCHLORIDE FILM-COATED TABLETS

Do not take Lercanidipine Hydrochloride film-coated tablets if you:

• are allergic (hypersensitive) to lercanidipine or to any of the ingredients in Lercanidipine Hydrochloride film-coated tablets
• have had allergic reactions to medicines closely related to lercanidipine (such as amlodipine, nicardipine, felodipine, isradipine, nifedipine or lacidipine)
• are suffering from certain heart diseases:
  * uncontrolled heart failure
  * an obstruction to flow of blood from the heart
  * unstable angina (angina at rest or progressively increasing)
  * if you have had heart attack less than one month ago
• have severe liver or kidney problems
• are pregnant, if you wish to become pregnant or if you are a woman of childbearing age and do not use any contraceptive method
• are breast-feeding
• are taking ciclosporin

• amiodarone or quinidine (medicines to treat a fast heart beat)
• metoprolol (a medicine to treat high blood pressure)
• simvastatin (a medicine for high cholesterol value).

Taking Lercanidipine Hydrochloride film-coated tablets with food and drink - You must not eat grapefruit or drink grapefruit juice as this may increase the effect of lercanidipine.

Alcohol should be avoided while taking Lercanidipine Hydrochloride film-coated tablets as combining the tablets with alcohol can cause dizziness/fainting, tiredness or weakness. This is because the medicine may lower your blood pressure considerably together with alcohol.

Pregnancy and breast-feeding - Ask your doctor for advice before taking any medicine. If you are taking lercanidipine and think that you may be pregnant, consult your doctor. Lercanidipine should not be used if you are pregnant, if you wish to become pregnant or if you are a woman of childbearing age and do not use any contraceptive method.

Lercanidipine Hydrochloride film-coated tablets should not be used if you are breast-feeding.

Driving and using machines - Lercanidipine Hydrochloride film-coated tablets have a negligible influence on the ability to drive or use machines. However, side effect such as dizziness, weakness, tiredness and rarely sleepiness may occur. You should be careful until you know how you react to Lercanidipine.
Important information about some of the ingredients of Lercanidipine Hydrochloride film-coated tablets - Lercanidipine Hydrochloride film-coated tablets contain lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE LERCANIDIPINE HYDROCHLORIDE FILM-COATED TABLETS

Always take Lercanidipine Hydrochloride film-coated tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is one Lercanidipine Hydrochloride 10 mg film-coated tablet daily at the same time each day. This is preferably in the morning at least 15 minutes before breakfast, because a high fat meal significantly increases your blood levels of the medicine. Your doctor may decide to increase your dose to one Lercanidipine Hydrochloride 20 mg film-coated tablet daily, if needed.

The tablets should preferably be swallowed whole with 1/2 glass of water. The tablets can be divided into equal halves.

Lercanidipine is not recommended for use in children and adolescents below 18 years.

If you take more lercanidipine than you should - immediately contact a doctor or the nearest hospital casualty department. Exceeding the correct dosage may cause your blood pressure to become too low, and your heart to beat irregularly or faster. It may also lead to unconsciousness.

5. HOW TO STORE LERCANIDIPINE HYDROCHLORIDE FILM-COATED TABLETS

Keep out of the reach and sight of children. Do not use Lercanidipine Hydrochloride film-coated tablets after the expiry date, which is stated on the carton after 'EXP'. The expiry date refers to the last day of that month.

Storage conditions:
Do not store above 25°C. Store in the original package in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Lercanidipine Hydrochloride film-coated tablets contain - The active substance is lercanidipine hydrochloride. One 10 mg film-coated tablet contains 10 mg lercanidipine hydrochloride, equivalent to 9.4 mg lercanidipine. One 20 mg film-coated tablet contains 20 mg lercanidipine hydrochloride, equivalent to 18.8 mg lercanidipine.

The other ingredients are:
Tablet core: Magnesium stearate, povidone, sodium starch glycolate (Type A), lactose monohydrate, microcrystalline cellulose.
Film-coating 10 mg tablets: Macrogol, polyvinyl alcohol, talc, titanium dioxide (E171), yellow iron oxide (E172).
Film-coating 20 mg tablets: Macrogol, polyvinyl...
If you forget to take your Lercanidipine Hydrochloride film-coated tablets - If you forget to take a dose of Lercanidipine Hydrochloride film-coated tablets then take it as soon as you remember, unless it is nearly time for your next dose. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, lercanidipine can cause side effects, although not everybody gets them.

Uncommon (occur in less than 1 out of 100 users): • headache • dizziness • faster heartbeats • awareness of the beating of the heart • flushing (temporary redness of the face and neck) • ankle swelling.

Rare (occur in less than 1 out of 1000 users): • sleepiness • weakness • tiredness • nausea • vomiting • diarrhoea • abdominal pain • indigestion • rash • muscle pain • passage of large amounts of urine • angina pectoris.

Very rare (occur in less than 1 out of 10,000 users): • fainting • allergic reaction • swelling of gums • increase in liver enzyme values (seen in blood tests) • fall in blood pressure which can cause dizziness • light-headedness or fainting • more frequent urination • chest pain and heart attack.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

oxide (E172), red iron oxide (E172).

What Lercanidipine Hydrochloride film-coated tablets look like and contents of the pack - Lercanidipine Hydrochloride 10 mg film-coated tablets are yellow, round, biconvex 6.5 mm film-coated tablets, scored on one side, and marked 'L' on the other side. Lercanidipine Hydrochloride 20 mg film-coated Tablets are pink, round, biconvex 8.5 mm film-coated tablets, scored on one side, and 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.

Pack sizes:
Blister packs containing:
Lercanidipine Hydrochloride 10 mg film-coated tablets: 7, 10, 14, 20, 28, 30, 35, 50, 56, 60, 98, 100 tablets.
Lercanidipine Hydrochloride 20 mg film-coated tablets: 7, 10, 14, 20, 28, 30, 35, 42, 50, 56, 60, 98, 100 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Caduceus Pharma Limited, 6th Floor, 94 Wigmore Street, London, W1U 3RF, UK.

Manufacturer:
Actavis hf. Reykjavikurvurberg 78, IS-220 Hafnarfjordur, Iceland.
Actavis Ltd, BLB016 Bulebel Industrial Estate, Zejtun ZTN 3000, Malta.

The distributor is: Generics [UK] Limited, Potters Bar, Hertfordshire, EN6 1TL.
Lercanidipine Hydrochloride 10 mg film-coated tablets
(lercanidipine hydrochloride)

One tablet contains: 10 mg lercanidipine hydrochloride, equivalent to 9.4 mg lercanidipine. **Contains:** lactose. See leaflet for further information. For oral use. Read the package leaflet before use. **Keep out of the reach and sight of children.** Do not store above 25°C. Store in the original package in order to protect from moisture.

PL 24668/0173-6

MA Holder: Caduceus Pharma Ltd, 6th Floor, 94 Wigmore Street, London, W1U SRF
Distributed by: Generics UK Ltd, Potters Bar, Herts, EN6 1TL

Affix Dispensing Label Here
Lercanidipine Hydrochloride 10 mg film-coated tablets
lercanidipine hydrochloride
28 film-coated tablets

One tablet contains 10mg lercanidipine hydrochloride, equivalent to 9.4mg lercanidipine.

Contains lactose. See leaflet for further information.
For oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Do not store above 25°C. Store in the original package in order to protect from moisture.

Caduceus Pharma Ltd
6th Floor, 94 Wigmore Street, London, W1U 3RF

Distributed by
Glenmark Generics (Europe) Ltd
The Old Sawmill, Hatfield Park, Hatfield, AL9 5PG

UKPAR Lercanidipine Hydrochloride 10mg and 20mg Film-Coated Tablets
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UKPAR Lercanidipine Hydrochloride 10mg and 20mg Film-Coated Tablets

Lercanidipine Hydrochloride 20 mg film-coated tablets
(lercanidipine hydrochloride)
28 film-coated tablets

20 mg

Lercanidipine Hydrochloride 20 mg film-coated tablets (lercanidipine hydrochloride)
28 film-coated tablets

Lercanidipine Hydrochloride 20 mg film-coated tablets (lercanidipine hydrochloride)
One tablet contains: 20 mg lercanidipine hydrochloride, equivalent to 18.8 mg lercanidipine. Contains: lactose. See leaflet for further information. For oral use. Read the packaging leaflet before use. Keep out of the reach and sight of children. Do not store above 25°C. Store in the original package in order to protect from moisture.

MA Holder: Cadenceus Pharma Ltd, 6th Floor, 94 Wigmore Street, London, W1U 3RF
Distributed by: Genomics [UK] Limited, Potters Bar, Herts, EN6 1TL

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