Public Assessment Report

Decentralised Procedure

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

(Lercanidipine hydrochloride)

Procedure No: UK/H/3812 & 4214/001-2/DC


JENSON PHARMACEUTICAL SERVICES LTD
LAY SUMMARY

On 09 March 2011, Austria, Belgium, Germany, Spain, Finland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Romania, and the UK agreed to grant Marketing Authorisations to Jenson Pharmaceutical Services Ltd for the medicinal products Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets (PL 17871/0063-4, 0111-2; UK/H/3812 & 4214/001-2/DC). These licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 06 April 2011. These are prescription-only medicines (POM) used to treat high blood pressure.

Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets belong to a group of medicines called calcium channel blockers. These work by opening up the blood vessels and increasing the flow of blood through them.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets outweigh the risks.
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Module 1

| **Product Name** | Lercanidipine Hydrochloride 10 mg film-coated tablets  
Lercanidipine Hydrochloride 20 mg film-coated tablets |
<table>
<thead>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Lercanidipine hydrochloride</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-coated tablet</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>10 mg and 20 mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Jenson Pharmaceutical Services Ltd, Carradine House, 237 Regents Park Road, London, N3 3LF, UK.</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
</tbody>
</table>
| **Concerned Member States (CMS)** | UK/H/3812/001-2/DC: Austria, Belgium, Germany, Spain, Finland, Ireland, the Netherlands, Norway, Portugal and Romania.  
UK/H/4214/001-2/DC: Belgium, Italy, Luxembourg and Portugal. |
| **Procedure Number** | UK/H3812 and 4214/001-2/DC |
| **Timetable** | Day 210 – 09 March 2011 |
Module 2
Summary of Product Characteristics

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg of lercanidipine hydrochloride, which is equivalent to 9.4 mg of lercanidipine.
Excipients – Contains Lactose Monohydrate 25.0 mg
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Yellowish brown, circular, biconvex tablets, scored on one 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 Hydrochloride is indicated for the treatment of mild to moderate essential hypertension.

4.2 Posology and method of administration
Method of administration:
Oral use
The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water)
The recommended dosage is 10 mg 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 Hydrochloride to therapy with a beta-adrenoreceptor blocking drug (atenolol), a diuretic (hydrochlorothiazide) or an angiotensin converting enzyme inhibitor (captopril or enalapril).
Since the dose-response curve is steep with a plateau at doses between 20-30 mg, it is unlikely that efficacy will be improved by higher doses; whereas side effects may increase.

Use in the elderly: although the pharmacokinetic data and clinical experience suggest that no adjustment of the daily dosage is required, special care should be exercised when initiating treatment in the elderly.

Use in children: Lercanidipine Hydrochloride is not recommended for use in children below 18 years due to insufficient data on safety and efficacy.

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 Hydrochloride is not recommended for use in patients with severe hepatic impairment or severe renal impairment (Glomerular Filtration Rate(GFR) < 30 ml/min).

4.3 Contraindications
Hypersensitivity to the active substance “lercanidipine” or to any dihydropyridine or to any of the excipients of the medicinal product.
• Pregnancy and lactation (see 4.6).
• Women of child-bearing potential unless effective contraception is used.
• Left ventricular outflow tract obstruction.
• Untreated congestive cardiac failure.
• Unstable angina pectoris.
• Severe renal or hepatic impairment.
• Within 1 month of a myocardial infarction.
• Co-administration with:
  • strong inhibitors of CYP3A4 (see 4.5),
  • ciclosporin (see 4.5),
  • grapefruit juice (see 4.5).

4.4 Special warnings and precautions for use

Special care should be exercised when Lercanidipine Hydrochloride 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 Hydrochloride is long-acting caution is required in such patients.

Some dihydropyridines may rarely lead to precordial pain or angina pectoris. Very rarely patients with pre-existing angina pectoris may experience increased frequency, duration or severity of these attacks. Isolated cases of myocardial infarction may be observed (see 4.8).

Use in 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 Hydrochloride 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).

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Lercanidipine Hydrochloride 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 Hydrochloride.

Co-prescription of Lercanidipine Hydrochloride 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 Hydrochloride (a 15-fold increase of the AUC and an 8-fold increase of the $C_{\text{max}}$ for the eutomer S-Lercanidipine).

Ciclosporin and Lercanidipine Hydrochloride should not be administered together (see 4.3).

Increased plasma levels of both Lercanidipine Hydrochloride 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 Hydrochloride intake, the plasma levels of Lercanidipine Hydrochloride did not change, while the AUC of ciclosporin increased by 27%.

However, the co-administration of Lercanidipine Hydrochloride with ciclosporin has caused a 3-fold increase of the plasma levels of Lercanidipine Hydrochloride and a 21% increase of the ciclosporin AUC. Lercanidipine Hydrochloride should not be taken with grapefruit juice (see 4.3).

As for other dihydropyridines, Lercanidipine Hydrochloride is sensitive to inhibition of metabolism by grapefruit juice, with a consequent rise in its systemic availability and increased hypotensive effect.
When concomitantly administered at a dose of 20 mg with midazolam p.o. to elderly volunteers, Lercanidipine's absorption was increased (by approximately 40%) and the rate of absorption was decreased (t\text{max} was delayed from 1.75 to 3 hours). Midazolam concentrations were not modified.

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

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

When Lercanidipine Hydrochloride was co-administered with metoprolol, a β-blocker eliminated mainly by the liver, the bioavailability of metoprolol was not changed while that of Lercanidipine Hydrochloride 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 Hydrochloride may be safely administered with beta-adrenoceptor blocking drugs, but dose adjustment may be required.

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

Concomitant administration of cimetidine 800 mg daily does not cause significant modifications in plasma levels of Lercanidipine Hydrochloride, but at higher doses caution is required since the bioavailability and the hypotensive effect of Lercanidipine Hydrochloride may be increased.

Co-administration of 20 mg Lercanidipine Hydrochloride in patients chronically treated with β-methyldigoxin showed no evidence of pharmacokinetic interaction. Healthy volunteers treated with digoxin following dosing with 20 mg Lercanidipine Hydrochloride 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.

When a dose of 20 mg of Lercanidipine Hydrochloride was repeatedly co-administered with 40 mg of simvastatin, the AUC of Lercanidipine Hydrochloride 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 Hydrochloride is administered in the morning and simvastatin in the evening, as indicated for such drug.

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

Lercanidipine Hydrochloride has been safely administered with diuretics and ACE inhibitors. Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive drugs (see 4.4).

**4.6 Pregnancy and lactation**

Data for Lercanidipine Hydrochloride provide no evidence of a teratogenic effect in the rat and the rabbit and reproductive performance in the rat was unimpaired. Nevertheless, since there is no clinical experience with Lercanidipine Hydrochloride in pregnancy and lactation, and other dihydropyridine compounds have been found teratogenic in animals, Lercanidipine Hydrochloride should not be administered during pregnancy or to women with child-bearing potential unless effective contraception is used. Because of high lipophilicity of Lercanidipine Hydrochloride, distribution in milk may be expected. Therefore, it should not be administered to nursing mothers.

**4.7 Effects on ability to drive and use machines**

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

About 1.8% of treated patients experienced adverse reactions. The table below shows the incidence of adverse drug reactions, at least possibly causally related, grouped by MedDRA system organ class and ranked by frequency (uncommon, rare).

The following terminologies have been used in order to classify the occurrence of undesirable effects:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

As shown in the table, the most commonly occurring adverse reactions reported in controlled clinical trials are headache, dizziness, peripheral oedema, tachycardia, palpitations, flushing, each occurring in less than 1% of patients.

<table>
<thead>
<tr>
<th>System Organs</th>
<th>Incidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Very rare</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Rare</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon</td>
<td>Headache; dizziness</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>Tachycardia; palpitations</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon</td>
<td>Flushing</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Rare</td>
<td>Nausea; dyspepsia; diarrhoea; abdominal pain; vomiting</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rare</td>
<td>Rash</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Rare</td>
<td>Myalgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Rare</td>
<td>Polyuria</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Uncommon</td>
<td>Oedema peripheral</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Asthenia; fatigue</td>
</tr>
</tbody>
</table>

In post-marketing experience, from spontaneous reports the following undesirable effects were reported very rarely (<1/10,000): gingival hypertrophy, reversible increases in serum levels of hepatic transaminases, hypotension, urinary frequency and chest pain.

Lercanidipine Hydrochloride 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.

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

4.9 Overdose

In the post-marketing experience, two cases of overdose were reported (150 mg and 280 mg of Lercanidipine, respectively, ingested in an attempt to commit suicide). The first patient developed sleepiness and was treated by gastric lavage. The second patient developed cardiogenic shock with severe myocardial ischaemia and mild renal failure and was treated with high-dose catecholamines, furosemide, digitalis and parenteral plasma expanders. Both cases resolved without sequelae.

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 Lercanidine, 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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective calcium channel blockers of dihydropyridine derivatives with mainly vascular effects ATC code: C08CA13

Lercanidine Hydrochloride 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, Lercanidine Hydrochloride 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 Lercanidine Hydrochloride 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 Lercanidine Hydrochloride is mainly due to its (S)-enantiomer.

In addition to the clinical studies conducted to support the therapeutic indications, a further small uncontrolled but randomised study of patients with severe hypertension (mean \(\pm\) SD diastolic blood pressure of \(114.5 \pm 3.7\) mmHg) showed that blood pressure was normalised in 40% of the 25 patients on 20 mg once daily dose and in 56% of 25 patients on 10 mg twice daily doses of Lercanidine. In a double-blind, randomized, controlled study versus placebo in patients with isolated systolic hypertension Lercanidine Hydrochloride was efficacious in lowering systolic blood pressure from mean initial values of \(172.6 \pm 5.6\) mmHg to \(140.2 \pm 8.7\) mmHg.

5.2 Pharmacokinetic properties

Absorption

Lercanidine Hydrochloride is completely absorbed after 10-20 mg oral administration and peak plasma levels, \(3.30\) ng/ml \(\pm 2.09\) s.d. and \(7.66\) ng/ml \(\pm 5.90\) s.d. respectively, occur about 1.5-3 hours after dosing.

The two enantiomers of Lercanidine Hydrochloride 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 Hydrochloride orally administered to patients under fed conditions is around 10%, although it is reduced to 1/3 when administered to healthy volunteers under fasting conditions.

Oral availability of Lercanidipine Hydrochloride increases 4-fold when Lercanidipine Hydrochloride is ingested up to 2 hours after a high fat meal. Accordingly, Lercanidipine Hydrochloride should be taken before meals.

**Distribution**

Distribution from plasma to tissues and organs is rapid and extensive.

The degree of serum protein binding of Lercanidipine Hydrochloride exceeds 98%. Since plasma protein levels are reduced in patients with severe renal or hepatic dysfunction, the free fraction of the drug may be increased.

**Biotransformation**

Lercanidipine Hydrochloride 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 Hydrochloride 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 Hydrochloride 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 Hydrochloride is not expected at therapeutic doses.

**Elimination**

Elimination occurs essentially by biotransformation.

A mean terminal elimination half life of 8-10 hours was calculated and the therapeutical activity lasts for 24 hours because of its high binding to lipid membrane. No accumulation was seen upon repeated administration.

**Linearity / non linearity**

Oral administration of Lercanidipine Hydrochloride leads to plasma levels of Lercanidipine Hydrochloride not directly proportional to dosage (non-linear kinetics). After 10, 20 or 40 mg, peak plasma concentrations observed were in the ratio 1:3:8 and areas under plasma concentration-time curves in the ratio 1:4:18, suggesting a progressive saturation of first pass metabolism. Accordingly, availability increases with dosage elevation.

**Characteristics in patients**

In elderly patients and in patients with mild to moderate renal dysfunction or mild to moderate hepatic impairment the pharmacokinetic behaviour of Lercanidipine Hydrochloride 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 Hydrochloride 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 Hydrochloride 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 Hydrochloride 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 Hydrochloride and/or its metabolites in pregnant animals and their excretion in breast milk have not been investigated.

Metabolites have not been evaluated separately in toxicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
- Lactose monohydrate
- Microcrystalline cellulose
- Crospovidone (type A)
- Povidone K30
- Magnesium stearate

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/opaque PVC blisters.

Packs of 7, 14, 28, 35, 50, 56, 98 and 100 tablets.*

*Not all pack sizes may be marketed.

HDPE Bottle with white opaque polypropylene cap of 500 and 1000 tablets.

Silica desiccant.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Ltd
Carradine House, 237 Regents Park Road,
London, N3 3LF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 17871/0063
PL 17871/0111

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/04/2011

10 DATE OF REVISION OF THE TEXT

06/04/2011
1 NAME OF THE MEDICINAL PRODUCT
Lercanidipine Hydrochloride 20 mg film-coated tablets

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Each tablet contains 20 mg of lercanidipine hydrochloride, which is equivalent to 18.8 mg of lercanidipine.
Excipients – Contains Lactose Monohydrate 50.0 mg
For a full list of excipients, see section 6.1.

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Film-coated tablet.
Pink, circular, biconvex tablets, scored on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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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 Hydrochloride to therapy with a beta-adrenoceptor blocking drug Beta-blocking agent (atenolol), a diuretic (hydrochlorothiazide) or an angiotensin converting enzyme inhibitor (captopril or enalapril).

Since the dose-response curve is steep with a plateau at doses between 20-30 mg, it is unlikely that efficacy will be improved by higher doses; whereas side effects may increase.

Use in the elderly: although the pharmacokinetic data and clinical experience suggest that no adjustment of the daily dosage is required, special care should be exercised when initiating treatment in the elderly.

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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 Hydrochloride is not recommended for use in patients with severe hepatic impairment or severe renal impairment (Glomerular Filtration Rate(GFR) < 30 ml/min).

4.3 Contraindications
Hypersensitivity to the active substance “lercanidipine” or to any dihydropyridine or to any of the excipients of the medicinal product.
• Pregnancy and lactation (see 4.6).
• Women of child-bearing potential unless effective contraception is used.
• Left ventricular outflow tract obstruction.
• Untreated congestive cardiac failure.
• Unstable angina pectoris.
• Severe renal or hepatic impairment.
• Within 1 month of a myocardial infarction.
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Lercanidipine Hydrochloride 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).

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Lercanidipine Hydrochloride 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 Hydrochloride.

Co-prescription of Lercanidipine Hydrochloride 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 Hydrochloride (a 15-fold increase of the AUC and an 8-fold increase of the C_max for the eutomer S-Lercanidipine).

Ciclosporin and Lercanidipine Hydrochloride should not be administered together (see 4.3).

Increased plasma levels of both Lercanidipine Hydrochloride 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 Hydrochloride intake, the plasma levels of Lercanidipine Hydrochloride did not change, while the AUC of ciclosporin increased by 27%.

However, the co-administration of Lercanidipine Hydrochloride with ciclosporin has caused a 3-fold increase of the plasma levels of Lercanidipine Hydrochloride and a 21% increase of the ciclosporin AUC. Lercanidipine Hydrochloride should not be taken with grapefruit juice (see 4.3).

As for other dihydropyridines, Lercanidipine Hydrochloride is sensitive to inhibition of metabolism by grapefruit juice, with a consequent rise in its systemic availability and increased hypotensive effect.
When concomitantly administered at a dose of 20 mg with midazolam p.o. to elderly volunteers, Lercanidipine's absorption was increased (by approximately 40%) and the rate of absorption was decreased ($t_{\text{max}}$ was delayed from 1.75 to 3 hours). Midazolam concentrations were not modified.

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

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

When Lercanidipine Hydrochloride was co-administered with metoprolol, a β-blocker eliminated mainly by the liver, the bioavailability of metoprolol was not changed while that of Lercanidipine Hydrochloride 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 Hydrochloride may be safely administered with beta-adrenoceptor blocking drugs, but dose adjustment may be required.

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

Concomitant administration of cimetidine 800 mg daily does not cause significant modifications in plasma levels of Lercanidipine Hydrochloride, but at higher doses caution is required since the bioavailability and the hypotensive effect of Lercanidipine Hydrochloride may be increased.

Co-administration of 20 mg Lercanidipine Hydrochloride in patients chronically treated with β-methyldigoxin showed no evidence of pharmacokinetic interaction. Healthy volunteers treated with digoxin following dosing with 20 mg Lercanidipine Hydrochloride 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 diogxin treatment should be closely monitored clinically for signs of digoxin toxicity.

When a dose of 20 mg of Lercanidipine Hydrochloride was repeatedly co-administered with 40 mg of simvastatin, the AUC of Lercanidipine Hydrochloride 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 Hydrochloride is administered in the morning and simvastatin in the evening, as indicated for such drug.

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

Lercanidipine Hydrochloride has been safely administered with diuretics and ACE inhibitors. Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive drugs (see 4.4).

### 4.6 Pregnancy and lactation

Data for Lercanidipine Hydrochloride provide no evidence of a teratogenic effect in the rat and the rabbit and reproductive performance in the rat was unimpaired. Nevertheless, since there is no clinical experience with Lercanidipine Hydrochloride in pregnancy and lactation, and other dihydropyridine compounds have been found teratogenic in animals, Lercanidipine Hydrochloride should not be administered during pregnancy or to women with child-bearing potential unless effective contraception is used. Because of high lipophilicity of Lercanidipine Hydrochloride, distribution in milk may be expected. Therefore, it should not be administered to nursing mothers.

### 4.7 Effects on ability to drive and use machines

Clinical experience with lercanidipine indicates that it is unlikely to impair a patient's ability to drive or use machinery. However, caution should be exercised because dizziness, asthenia, fatigue and rarely somnolence may occur.
4.8 Undesirable effects
About 1.8% of treated patients experienced adverse reactions.
The table below shows the incidence of adverse drug reactions, at least possibly causally related, grouped by MedDRA system organ class and ranked by frequency (uncommon, rare).

The following terminologies have been used in order to classify the occurrence of undesirable effects:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

As shown in the table, the most commonly occurring adverse reactions reported in controlled clinical trials are headache, dizziness, peripheral oedema, tachycardia, palpitations, flushing, each occurring in less than 1% of patients.

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th>Very rare</th>
<th>Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td>Rare</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon</td>
<td>Headache; dizziness</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>Tachycardia; palpitations</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon</td>
<td>Flushing</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Syncope</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Rare</td>
<td>Nausea; dyspepsia; diarrhoea; abdominal pain; vomiting</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rare</td>
<td>Rash</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Rare</td>
<td>Myalgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Rare</td>
<td>Polyuria</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Uncommon</td>
<td>Oedema peripheral</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Asthenia; fatigue</td>
</tr>
</tbody>
</table>

In post-marketing experience, from spontaneous reports the following undesirable effects were reported very rarely ( <1/10,000): gingival hypertrophy, reversible increases in serum levels of hepatic transaminases, hypotension, urinary frequency and chest pain.

Lercanidipine Hydrochloride 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.

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

4.9 Overdose
In the post-marketing experience, two cases of overdose were reported (150 mg and 280 mg of Lercanidipine, respectively, ingested in an attempt to commit suicide). The first patient developed sleepiness and was treated by gastric lavage. The second patient developed cardiogenic shock with severe myocardial ischaemia and mild renal failure and was treated with high-dose catecholamines, furosemide, digitalis and parenteral plasma expanders. Both cases resolved without sequelae.

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.

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group:
Selective calcium channel blockers of dihydropyridine derivatives with mainly vascular effects
ATC code: C08CA13
Lercanidipine Hydrochloride 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 Hydrochloride 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 Hydrochloride 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 Hydrochloride 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 Hydrochloride 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 Hydrochloride 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 Hydrochloride 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 Hydrochloride orally administered to patients under fed conditions is around 10%, although it is reduced to 1/3 when administered to healthy volunteers under fasting conditions.
Oral availability of Lercanidipine Hydrochloride increases 4-fold when Lercanidipine Hydrochloride is ingested up to 2 hours after a high fat meal. Accordingly, Lercanidipine Hydrochloride should be taken before meals.

**Distribution**
Distribution from plasma to tissues and organs is rapid and extensive.

The degree of serum protein binding of Lercanidipine Hydrochloride exceeds 98%. Since plasma protein levels are reduced in patients with severe renal or hepatic dysfunction, the free fraction of the drug may be increased.

**Biotransformation**
Lercanidipine Hydrochloride 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 Hydrochloride 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 Hydrochloride 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 Hydrochloride is not expected at therapeutic doses.

**Elimination**
Elimination occurs essentially by biotransformation.

A mean terminal elimination half life of 8-10 hours was calculated and the therapeutical activity lasts for 24 hours because of its high binding to lipid membrane. No accumulation was seen upon repeated administration.

**Linearity / non linearity**
Oral administration of Lercanidipine Hydrochloride leads to plasma levels of Lercanidipine Hydrochloride not directly proportional to dosage (non-linear kinetics). After 10, 20 or 40 mg, peak plasma concentrations observed were in the ratio 1:3:8 and areas under plasma concentration-time curves in the ratio 1:4:18, suggesting a progressive saturation of first pass metabolism. Accordingly, availability increases with dosage elevation.

**Characteristics in patients**
In elderly patients and in patients with mild to moderate renal dysfunction or mild to moderate hepatic impairment the pharmacokinetic behaviour of Lercanidipine Hydrochloride 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 Hydrochloride 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 Hydrochloride 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 Hydrochloride 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 Hydrochloride and/or its metabolites in pregnant animals and their excretion in breast milk have not been investigated. Metabolites have not been evaluated separately in toxicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core:
- Lactose monohydrate
- Microcrystalline cellulose
- Crospovidone (type A)
- Povidone K30
- Magnesium stearate

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

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Aluminium/opaque PVC blisters.
Packs of 7, 14, 28, 35, 50, 56, 98 and 100 tablets.*
*Not all pack sizes may be marketed.
HDPE Bottle with white opaque polypropylene cap of 500 and 1000 tablets.
Silica desiccant.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORITY Holder
Jenson Pharmaceutical Services Ltd
Carradine House, 237 Regents Park Road,
London, N3 3LF
United Kingdom

8 MARKETING AUTHORITY NUMBER(S)
PL 17871/0064
PL 17871/0112

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/04/2011

10 DATE OF REVISION OF THE TEXT
06/04/2011
Module 3

The following leaflets for Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets (PL 17871/0063 and PL 17871/0064 respectively) are included as representative example leaflets. The leaflets proposed for the products PL 17871/0111 and 0112 are consistent with these leaflets:

Take special care with Lercanidipine Hydrochloride
You should tell your doctor before taking this medicine, if you have:
• certain other heart conditions e.g. angina pectoris
• mild or moderate kidney or liver problems.

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. Very rare cases of myocardial infarction may be observed.

Taking 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, herbal medicines or any of the following:
• beta-blockers, diuretics or ACE inhibitors, medicines to treat high blood pressure although these may be safely taken with lercanidipine hydrochloride, some dosage adjustment may be needed
• clopidogrel, more than 800 mg, a medicine for ulcers, indigestion, or heartburn
• digoxin a medicine to treat a heart problem
• midazolam a medicine that helps you sleep
• rifampicin a medicine to treat tuberculosis
• nitrazepam a medicine that helps you sleep
• terfenadine or astemizole a medicine for allergies
• amiodarone or quinidine medicines to treat a fast heart beat
• phenytoin or carbamazepine medicines for epilepsy

Taking Lercanidipine Hydrochloride with food and drink
• Drinking alcohol during your treatment with Lercanidipine Hydrochloride tablets may increase the effect of Lercanidipine Hydrochloride tablets, you are therefore advised to avoid drinking alcohol while taking Lercanidipine Hydrochloride.

Pregnancy and breast-feeding
Do not take Lercanidipine Hydrochloride if you are pregnant or plan to become pregnant, as it can affect the development of your unborn baby.

Do not breast-feed if you are taking Lercanidipine Hydrochloride as it can pass into breast milk.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Do not drive or use machines if you suffer from dizziness, weakness or tiredness, while taking Lercanidipine Hydrochloride.

Important information about some of the ingredients of Lercanidipine Hydrochloride
These tablets contain lactose. If your doctor has told you that you have an intolerance to lactose, galactosaemia or glucose/galactose malabsorption syndrome, contact your doctor before taking this medicine.
3. HOW TO TAKE LERCANIDIPINE HYDROCHLORIDE

Dosage
Always take Lercanidipine Hydrochloride 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, preferably in the morning at least 15 minutes before breakfast. Your doctor may advise you to increase the dose to one Lercanidipine Hydrochloride 20 mg film-coated tablet daily, if needed.

The tablets should be swallowed whole with some water. This medicine should not be used in children under 18 years of age.

If you take more Lercanidipine Hydrochloride Tablets
Taking too many Lercanidipine Hydrochloride tablets can cause a severe drop in blood pressure, a slow heart rate and unconsciousness. If you take more tablets than you should contact your doctor or hospital immediately. Take any remaining tablets or this leaflet with you so the medical staff know exactly what you have taken.

If you forget to take Lercanidipine Hydrochloride
If you forget to take a tablet, take it if you remember within 12 hours of your usual time. If more than 12 hours have passed, you should not take the missed tablet but should take your next tablet as the normal time when it is due.

If you stop taking Lercanidipine Hydrochloride
Do not stop taking your tablets suddenly as your condition may get worse.

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

4. POSSIBLE SIDE EFFECTS

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

Uncommon side effects (affecting less than 1 in 100 patients):
- headache
- dizziness
- faster heart beats
- awareness of the beating of the heart
- redness of the skin
- swelling of the hands and feet.

Rare side effects (affecting less than 1 in 1,000 of patients):
- sleepiness
- chest pain
- nausea and vomiting
- diarrhoea
- rash
- muscle pain
- passage of large amounts of urine
- tiredness and weakness
- indigestion and stomach pain.

Very rare side effects (affecting less than 1 out 10,000 of patients):
- swelling of gums
- increase in blood test values which show changes in the way the liver is working
- fall in blood pressure which can cause dizziness
- increase in the usual number of times you need to pass urine
- isolated cases of heart attack have been reported.

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.

5. HOW TO STORE LERCANIDIPINE HYDROCHLORIDE

Keep out of the reach and sight of children. Do not use Lercanidipine Hydrochloride after the expiry date which is stated on both the outer carton and on each blister strip of tablets. The expiry date refers to the last day of that month. This medicinal product does not require any special storage conditions. 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 contains
The active substance is lercanidipine hydrochloride. The other ingredients are Lactose monohydrate, Microcrystalline cellulose, crospovidone (type A), Povidone K30, Magnesium stearate, Film coating: Hypromellose, Titanium dioxide (E171), Iron oxide yellow (E172) Macrogol 8000, Iron oxide red (E172), Iron oxide black (E172).

What Lercanidipine Hydrochloride looks like and contents of the pack
Lercanidipine Hydrochloride 10mg Film-coated tablets are circular, biconvex tablets, Yellowish brown in colour.

Lercanidipine Hydrochloride 10 mg film-coated tablets come in packs of 7, 14, 28, 35, 50, 56, 98 and 100 tablets. HDPE Bottle of 500 film-coated tablets and 1000 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Jenson Pharmaceutical Services Limited, Camadine House, 237 Regent's Park Road, London, N3 3LF, United Kingdom.

Manufacturer:
McDemott Laboratories Limited trading as Gerard Laboratories, 35/96 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland.
PACKAGE LEAFLET INFORMATION FOR THE USER

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

Read all of this leaflet carefully before you start taking 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 is and what it is used for.
2. Before you take Lercanidipine Hydrochloride.
3. How to take Lercanidipine Hydrochloride.
4. Possible side effects.
5. How to store Lercanidipine Hydrochloride.
6. Further information.

1. WHAT LERCANIDIPINE HYDROCHLORIDE IS AND WHAT IT IS USED FOR

Lercanidipine Hydrochloride belongs to a group of medicines called calcium channel blockers which are used to treat high blood pressure. Lercanidipine Hydrochloride works by opening up the blood vessels and increasing the flow of blood through them.

2. BEFORE YOU TAKE LERCANIDIPINE HYDROCHLORIDE

Do not take Lercanidipine Hydrochloride:
- If you are allergic (hypersensitive) to lercanidipine hydrochloride or any of the other ingredients in the tablets.
- If you have had allergic reactions to drugs closely related to Lercanidipine Hydrochloride tablets (such as amiodipine, nicardipine, felodipine, lisinopirine, nifedipine or lacidipine).
- If you are pregnant or breast-feeding, or if you intend to become pregnant or do not use an effective contraceptive.
- If you are suffering from certain heart diseases:
  * Uncontrolled cardiac failure
  * Obstruction to flow of blood from the heart
  * Unstable angina (angina at rest or progressively increasing)
  * Within one month of heart attack
  * If you have severe liver or kidney problems.
- If you are taking the following drugs/food:
  * Antifungal medicines (such as ketoconazole or itraconazole)
  * Macrolide antibiotics (such as erythromycin or troleandomycin)
  * Antivirals (such as ritonavir, a medicine to treat AIDS)
  * Ciclosporin (a medicine used to prevent rejection after a transplant)
  * Grapefruit or grapefruit juice.

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You should tell your doctor before taking this medicine, if you have:
- Certain other heart conditions e.g. angina pectoris
- Mild or moderate kidney or liver problems.

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. Very rare cases of myocardial infarction may be observed.

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Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, herbal medicines or any of the following:
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- Cimetidine, more than 800 mg, a medicine for ulcers, indigestion, or heartburn.
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- Midazolam a medicine that helps you sleep.
- Rifampicin a medicine to treat tuberculosis.
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- Terfenadine or astemizole a medicine for allergies.
- Amiodarone or quinidine medicines to treat a fast heart beat.
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Do not take Lercanidipine Hydrochloride if you are pregnant or plan to become pregnant, as it can affect the development of your unborn baby.

Do not breast-feed if you are taking Lercanidipine Hydrochloride as it can pass into breast milk.

Ask your doctor or pharmacist for advice before taking any medicine.

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Do not drive or use machines if you suffer from dizziness, weakness or tiredness, while taking Lercanidipine Hydrochloride.

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If you stop taking Lercanidipine Hydrochloride
Do not stop taking your tablets suddenly as your condition may get worse.

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

4. POSSIBLE SIDE EFFECTS

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

Uncommon side effects (affecting less than 1 out 100 patients):
- headache
- dizziness
- faster heart beats
- awareness of the beating of the heart
- redness of the skin
- swelling of the hands and feet.

Rare side effects (affecting less than 1 out 1,000 of patients):
- sleepiness
- chest pain
- nausea and vomiting
- diarrhoea
- rash
- muscle pain
- passage of large amounts of urine
- tiredness and weakness
- indigestion and stomach pain.

Very rare side effects (affecting less than 1 out 10,000 of patients):
- swelling of gums
- increase in blood test values which show changes in the way the liver is working
- fall in blood pressure which can cause dizziness
- increase in the usual number of times you need to pass urine
- isolated cases of heart attack have been reported.

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.

5. HOW TO STORE LERCANIDIPINE HYDROCHLORIDE

Keep out of the reach and sight of children. Do not use Lercanidipine Hydrochloride after the expiry date which is stated on both the outer carton and on each blister strip of tablets. The expiry date refers to the last day of that month. This medicinal product does not require any special storage conditions. 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 contains
The active substance is Lercanidipine hydrochloride. The other ingredients are Lactose monohydrate, Microcrystalline cellulose, crospovidone (type A), Povidone K30, Magnesium stearate, Film coating: Hypromellose, Titanium dioxide (E171), Macrogol 8000, Iron oxide yellow (E172), Iron oxide red (E172).

What Lercanidipine Hydrochloride looks like and contents of the pack
Lercanidipine Hydrochloride 10 mg film-coated tablets are circular, biconvex tablets, pink in colour. Lercanidipine 20 mg tablets come in packs of 7, 14, 28, 35, 50, 60, 98 and 100 tablets. HOPE Bottle of 500 film-coated tablets and 1000 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Jenson Pharmaceutical Services Limited, Carradine House, 237 Regent's Park Road, London, N3 3LF, United Kingdom.

Manufacturer:
McDermott Laboratories Limited trading as Gerard Laboratories, 35/36 Baldyke Industrial Estate, Grange Road, Dublin 13, Ireland.

This leaflet was last updated on: April 2011
Module 4
Labelling

The following labelling for Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets (PL 17871/0063 and PL 17871/0064 respectively) are included as representative example labelling. The labelling proposed for the products PL 17871/0111 and 0112 are consistent with this labelling:

Carton:
Blister:
Blister:
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets (PL 17871/0063-4, 0111-2; UK/H/3812 & 4214/001-2/DC) could be approved. These applications were submitted by the Decentralised Procedure, with the UK as Reference Member State (RMS), and Austria, Belgium, Germany, Spain, Finland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal and Romania, as Concerned Member States (CMS).

Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets are prescription-only medicines (POM) indicated for the treatment of mild to moderate essential hypertension.

These are applications made according to Article 10.1 of 2001/83/EC, as amended, claiming to be generic versions of medicinal product Zanidip 10 mg and 20 mg film-coated tablets (Recordati Industria Chimica e Farmaceutica S.p.A, Italy) which was first authorised in the UK on 22 March 1996.

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.

No new non-clinical studies were conducted, which is acceptable given that the applications were for products that are being considered as generic medicinal products and the originator product has been licensed for over 10 years.

One single-dose, bioequivalence study was submitted to support these applications, comparing the test product Lercanidipine Hydrochloride 20 mg film-coated tablets with the reference product Zanidip 20 mg film-coated tablets (Recordati Industria Chimica e Farmaceutica S.p.A). With the exception of this bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were for products that are being considered as generic medicinal products and the originator product has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved, with the end of procedure (Day 210) on 09 March 2011. After a subsequent national phase, the licences were granted in the UK on 06 April 2011
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Lercanidipine Hydrochloride 10 mg film-coated tablets  
Lercanidipine Hydrochloride 20 mg film-coated tablets |
<table>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Lercanidipine hydrochloride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Selective calcium channel blockers with mainly vascular effects (C08CA13)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>10 mg and 20 mg film-coated tablets</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H3812 and 4214/001-2/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>
| Member States concerned                      | UK/H3812/001-2/DC: Austria, Belgium, Germany, Spain, Finland, Ireland, the Netherlands, Norway, Portugal and Romania.  
UK/H4214/001-2/DC: Belgium, Italy, Luxembourg and Portugal. |
| Marketing Authorisation Number(s)            | PL 17871/0063-4 and 0111-2                      |
| Name and address of the authorisation holder  | Jenson Pharmaceutical Services Ltd,  
Carradine House, 237 Regents Park Road,  
London, N3 3LF, UK                              |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

S.  Active substance

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 of Lercanidipine Hydrochloride](image)

Molecular formula:  C_{36}H_{41}N_{3}O_{6} \cdot \text{HCl}
Molecular weight:  648.19
Appearance:  Lercanidipine hydrochloride (crystalline form) is a yellow powder soluble in methanol and practically insoluble in water.

Lercanidipine hydrochloride was not the subject of a European Pharmacopoeia monograph at the time of assessment.

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.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

P.  Medicinal Product

Other Ingredients

Other ingredients consist of the following pharmaceutical excipients lactose monohydrate, microcrystalline cellulose, crospovidone (type A), povidone K30 and magnesium stearate. In addition:
- the 10 mg strength contains Opadry yellow 03F82659 (comprised of hypromellose, titanium dioxide (E171), iron oxide yellow (E172), macrogol 8000, iron oxide red (E172) and iron oxide black [E172]).
- the 20 mg strength contains Opadry pink 03F84645 (comprised of hypromellose, titanium dioxide (E171), iron oxide yellow (E172), macrogol 8000 and iron oxide red [E172]).

All excipients comply with their respective European Pharmacopoeia monograph with the exception of Opadry yellow 03F82659 and Opadry pink 03F84645 which are compliant with suitable in-house specifications. In addition, the specifications for Opadry yellow 03F82659 and Opadry pink 03F84645 are in compliance with Directive 78/25/EC (concerning use of colouring agents in foodstuff). Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to formulate robust, stable tablets containing 10 mg and 20 mg lercanidipine hydrochloride that could be considered as generic medicinal products of Zanidip 10 mg and 20 mg film-coated tablets (Recordati Industria Chimica e Farmaceutica S.p.A). A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and these comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
The finished products are packaged in the following presentations:
- aluminium/opaque polyvinylchloride blisters in pack sizes of 7, 14, 28, 35, 50, 56, 98 and 100 tablets.
- HDPE bottles with a white opaque polypropylene cap in pack sizes of 500 and 1000 tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.
Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the Product**
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with no special storage conditions.

**Bioequivalence/bioavailability**
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labels are acceptable.

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 leaflet conforms to the requirements. The test shows that the patients/users are able to act upon the information that the leaflet contains.

**MAA Forms**
The MAA forms are satisfactory.

**Expert Report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

**III.2 NON-CLINICAL ASPECTS**
As the pharmacodynamic, pharmacokinetic and toxicological properties of lercanidipine hydrochloride are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a non-clinical viewpoint.
III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open label, balanced, randomised, two-treatment, four period, two-sequence, replicate, single dose, crossover study to compare the pharmacokinetics of the test product Lercanidipine Hydrochloride 20 mg film-coated tablets (Jenson Pharmaceutical Services Ltd) versus the reference product Zanidip 20 mg film-coated tablets (Recordati Industria Chimica e Farmaceutica S.p.A) in healthy adult male volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 36 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for R-lercanidipine presented below (geometric Least Squares Mean, ratios and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt;</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt;</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>22.101 ng/ml/h</td>
<td>23.257 ng/ml/h</td>
<td>4.097 ng/ml</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>20.660 ng/ml/h</td>
<td>21.778 ng/ml/h</td>
<td>4.040 ng/ml</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>107.0 (98.50-116.18%)</td>
<td>106.8 (98.52-115.75%)</td>
<td>101.4 (91.87-111.92%)</td>
</tr>
</tbody>
</table>

AUC<sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity
AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours
C<sub>max</sub> maximum plasma concentration

*ln-transformed values

The pharmacokinetic results for S-lercanidipine presented below (geometric Least Squares Mean, ratios and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt;</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt;</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>20.763 ng/ml/h</td>
<td>21.826 ng/ml/h</td>
<td>4.121 ng/ml</td>
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<tr>
<td>Reference (mean)</td>
<td>19.536 ng/ml/h</td>
<td>20.545 ng/ml/h</td>
<td>4.108 ng/ml</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>106.3 (98.00-115.27%)</td>
<td>106.2 (98.20-114.93%)</td>
<td>100.3 (90.92-110.67%)</td>
</tr>
</tbody>
</table>

AUC<sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity
AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours
C<sub>max</sub> maximum plasma concentration

*ln-transformed values

The 90% confidence intervals for AUC and C<sub>max</sub> for test versus reference product for both enantiomers R-lercanidipine and S-lercanidipine are within predefined acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1). Thus, the data support the claim that the test product is bioequivalent to the reference product.

As the 10 mg and 20 mg strengths of the product meet the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence...
(CPMP/EWP/QWP/1401/98 Rev1), the results and conclusions of the bioequivalence study on the 20 mg strength can be extrapolated to the 10 mg strength.

**Pharmacodynamics**
No new pharmacodynamic data were submitted and none were required for these applications.

**Efficacy**
No new efficacy data were submitted and none were required for these applications.

**Safety**
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were raised by the bioequivalence data.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labels are acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the SmPC and in-line with current guidelines. The labelling is in-line with current guidelines.

**Clinical Expert Report**
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Pharmacovigilance System and Risk Management Plan**
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for these products.

**Conclusion**
There are no objections to the approval of these applications from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Lercanidipine Hydrochloride 10 mg and 20 mg 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of lercanidipine hydrochloride are well-known.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Lercanidipine Hydrochloride 20 mg film-coated tablets and its respective reference product (Zanidip 20 mg film-coated tablets). As the 10mg strength of the product meet the biowaiver criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions of the bioequivalence study on the 20 mg strength can be extrapolated to the 10 mg strength tablet.

SAFETY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of lercanidipine hydrochloride is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference product, where appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s product and the originator product are interchangeable. Extensive clinical experience with lercanidipine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
## Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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