

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

**PL 25258/0087-8**

**UK PAR**

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

**PL 25258/0087-8**

**LAY SUMMARY**

The MHRA granted Glenmark Generics (Europe) Ltd Marketing Authorisations (licences) for the medicinal products Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets on 11 October 2011. These are prescription-only medicines (POM) used in the treatment of mild to moderate high blood pressure, known as hypertension.

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. 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.

These applications are duplicates of previously granted applications for Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets (PL 24668/0173-4), which were granted to the Marketing Authorisation Holder Caduceus Pharma Limited on 22 December 2009.

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

**LERCANIDIPINE HYDROCHLORIDE 10 MG FILM-COATED TABLETS  
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**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the MHRA granted Marketing Authorisations for the medicinal products Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets (PL 25258/0087-8) to Glenmark Generics (Europe) Ltd on 11 October 2011. These are prescription-only medicines (POM) indicated for the treatment of mild to moderate essential hypertension.

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.

These applications were submitted as simple abridged applications according to Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC, cross-referring to Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets (PL 24668/0173-4) approved on 22 December 2009 to the Marketing Authorisation Holder Caduceus Pharma Limited.

No new data were submitted nor were they necessary for these simple applications, as the data are identical to that of the previously granted cross-reference products.

## **PHARMACEUTICAL ASSESSMENT**

**LICENCE NO:** PL 25258/0087-8  
**PROPRIETARY NAME:** Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets  
**COMPANY NAME:** Glenmark Generics (Europe) Ltd  
**E.C. ARTICLE:** Article 10(c) of Directive 2001/83/EC  
**LEGAL STATUS:** POM

### **1 INTRODUCTION**

These are simple, informed consent applications for Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets submitted under Article 10(c) of Directive 2001/83/EC. The applications cross-refer to Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets (PL 24668/0173-4) approved on 22 December 2009, to Caduceus Pharma Limited.

The current applications are considered valid.

### **2 MARKETING AUTHORISATION APPLICATION (MAA)**

#### **2.1 Name(s)**

The proposed names of the product are Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets. The product has been named in line with current requirements.

#### **2.2 Strength, pharmaceutical form, route of administration, container and pack sizes**

The product contains lercanidipine hydrochloride 10 mg or 20 mg and is packaged in aluminium/polyvinylchloride blisters with push-through foil in pack sizes of 7, 10, 14, 20, 28, 30, 35, 42 (20 mg only), 50, 56, 60, 98, 100 film-coated 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.

The proposed shelf life is 2 years with the advice to 'Store below 25°C. Store in the original package in order to protect from moisture.'

The proposed shelf-life and storage conditions are consistent with the details registered for the cross-referenced products.

#### **2.3 Legal status**

On approval, the products will be available by supply through pharmacies, subject to a medical prescription (POM).

#### **2.4 Marketing Authorisation Holder/Contact Persons/Company**

The proposed Marketing Authorisation Holder is Glenmark Generics (Europe) Ltd, Laxmi House, 2 B Draycott Avenue, Kenton, Middlesex, HA3 0BU, UK.

The Qualified Person (QP) responsible for pharmacovigilance is stated and their CV is included.

#### **2.5 Manufacturers**

The proposed manufacturing site is consistent with that registered for the reference products and evidence of compliance with current Good Manufacturing Practice has been provided.

## **2.6 Qualitative and quantitative composition**

The compositions are consistent with the details registered for the reference products.

## **2.7 Manufacturing process**

The manufacturing process is consistent with the details registered for the reference products.

## **2.8 Finished product/shelf-life specification**

The finished product specifications are in line with the details registered for the reference products.

## **2.9 Drug substance specification**

The drug substance specifications are consistent with the details registered for the cross-reference products.

## **2.10 TSE Compliance**

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption.

This is consistent with the reference products.

## **2.11 Bioequivalence**

No bioequivalence data are required to support these informed consent applications, as the proposed products are manufactured to the same formula utilising the same process as the reference products Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets (PL 24668/0173-4).

## **3 EXPERT REPORT**

The applicant has included a detailed pharmaceutical expert report, written by an appropriately qualified person.

## **4. PRODUCT NAME & APPEARANCE**

See 2.1 for details of the proposed product names. The appearance of the products is identical to that of the reference products.

## **5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)**

The proposed SmPCs are consistent with the details registered for the reference products.

## **6. PATIENT INFORMATION LEAFLET (PIL)/LABELLING**

### PIL

The patient information leaflet has been prepared in line with the details registered for the reference products.

### Carton and blister

The proposed artwork complies with the relevant statutory requirements. In line with current legislation, the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

## **7. CONCLUSIONS**

The data submitted with these applications is acceptable. The grant of Marketing Authorisations is recommended.

## **NON-CLINICAL ASSESSMENT**

As these applications are identical to the reference products Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets (PL 24668/0173-4), no new non-clinical data have been supplied with these applications and none are required. A non-clinical expert report has been written by a suitably qualified person and is satisfactory.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environment Risk Assessment (ERA). As these applications are for identical versions of already authorised reference products, it is not expected that the environmental exposure to lercanidipine will increase following the marketing approval of the proposed products.

## **CLINICAL ASSESSMENT**

As these applications are identical to the reference products Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets (PL 24668/0173-4), no new clinical data have been supplied with these applications and none are required. A clinical expert report has been written by a suitably qualified person and is satisfactory.

The Marketing Authorisation Holder has provided a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that the Marketing Authorisation Holder 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.

## **OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT**

### **QUALITY**

The data for these applications are consistent with that previously assessed for the reference products and as such have been judged to be satisfactory.

### **NON-CLINICAL**

No new non-clinical data were submitted and none are required for applications of this type.

### **EFFICACY**

These applications are identical to the previously granted applications for Lercanidipine Hydrochloride 10 mg and 20 mg film-coated tablets (PL 24668/0173-4), granted to Caduceus Pharma Limited on 22 December 2009.

### **SAFETY**

No new or unexpected safety concerns arise from these applications.

### **PRODUCT LITERATURE**

The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference products.

Colour mock-ups of the labelling have been provided and are satisfactory. The approved labelling artwork complies with statutory requirements. The name of the product in Braille appears on the outer packaging.

### **BENEFIT/RISK ASSESSMENT**

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant's products are identical to the reference products. Extensive clinical experience with lercanidipine is considered to have demonstrated the therapeutic values of the compound. The benefit/risk is therefore considered to be positive.

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**STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the Marketing Authorisation Applications on 28 January 2011.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 17 February 2011.
3	Following assessment of the applications the MHRA requested further information on 09 May 2011, 30 June 2011 and 29 August 2011.
4	The applicant responded to the MHRA's request, providing further information on 07 June 2011, 26 July 2011 and 05 October 2011.
5	The applications were determined on 11 October 2011.

## 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 C<sub>max</sub> for the eutomer S-lercanidipine).

Increased plasma levels of both lercanidipine and ciclosporin have been observed following concomitant administration. A study in young healthy volunteers has shown that when ciclosporin was administered 3 hours after the lercanidipine intake, the plasma levels of lercanidipine did not change, while the AUC of ciclosporin increased by 27%. However, the co-administration of lercanidipine with ciclosporin has caused a 3-fold increase of the plasma levels of lercanidipine and a 21% increase of the ciclosporin AUC. Ciclosporin and lercanidipine should not be administered together.

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

When concomitantly administered at a dose of 20 mg with midazolam p.o. to elderly volunteers, lercanidipine's absorption was increased (by approximately 40%) and the rate of absorption was decreased ( $t_{max}$  was delayed from 1.75 to 3 hours). Midazolam concentrations were not modified.

#### CYP3A4 inducers

Co-administration of lercanidipine with CYP3A4 inducers like anticonvulsants (e.g. phenytoin, carbamazepine), 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  $C_{max}$ , 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 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  $65 \pm 7$  years (mean  $\pm$  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:	$\geq 1/10$
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).

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

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  $\pm$  SD diastolic blood pressure of  $114.5 \pm 3.7$  mmHg) showed that blood pressure was normalised in 40% of the 25 patients on 20 mg once daily dose and in 56% of 25 patients on 10 mg twice daily doses of lercanidipine. In a double-blind, randomized, controlled

study versus placebo in patients with isolated systolic hypertension lercanidipine was efficacious in lowering systolic blood pressure from mean initial values of  $172.6 \pm 5.6$  mmHg to  $140.2 \pm 8.7$  mmHg.

## 5.2 Pharmacokinetic properties

### *Absorption*

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

The two enantiomers of lercanidipine show a similar plasma level profile: the time to peak plasma concentration is the same, the peak plasma concentration and AUC are, on average, 1.2-fold higher for the (S) enantiomer and the elimination half-lives of the two enantiomers are essentially the same. No "in vivo" interconversion of enantiomers is observed.

Due to the high first pass metabolism, the absolute bioavailability of lercanidipine orally administered to patients under fed conditions is around 10%, although it is reduced to 1/3 when administered to healthy volunteers under fasting conditions.

Oral 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 therapeutic 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.

### 6.5 **Nature and contents of container**

Blister pack (Aluminium/PVC) 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**

GLENMARK GENERICS (EUROPE) LTD

LAXMI HOUSE, 2 B DRAYCOTT AVENUE,  
KENTON, MIDDLESEX,  
HA3 0BU  
UNITED KINGDOM

- 8**     **MARKETING AUTHORISATION NUMBER(S)**  
PL 25258/0087
- 9**     **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
11/10/2011
- 10**    **DATE OF REVISION OF THE TEXT**  
11/10/2011

**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.

### 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 ( $t_{max}$  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  $C_{max}$ , 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 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  $65 \pm 7$  years (mean  $\pm$  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:	$\geq 1/10$
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).

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

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  $\pm$  SD diastolic blood pressure of  $114.5 \pm 3.7$  mmHg) showed that blood pressure was normalised in 40% of the 25 patients on 20 mg once daily dose and in 56% of 25 patients on 10 mg twice daily doses of lercanidipine. In a double-blind, randomized, controlled study versus placebo in patients with isolated systolic hypertension lercanidipine was efficacious in lowering systolic blood pressure from mean initial values of  $172.6 \pm 5.6$  mmHg to  $140.2 \pm 8.7$  mmHg.

### 5.2 Pharmacokinetic properties

*Absorption*

Lercanidipine is completely absorbed after 10-20 mg oral administration and peak plasma levels,  $3.30 \text{ ng/ml} \pm 2.09 \text{ s.d.}$  and  $7.66 \text{ ng/ml} \pm 5.90 \text{ s.d.}$  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 therapeutic 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.

### **6.5 Nature and contents of container**

Blister pack (Aluminium/PVC) 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**

GLENMARK GENERICS (EUROPE) LTD  
LAXMI HOUSE, 2 B DRAYCOTT AVENUE,  
KENTON, MIDDLESEX,  
HA3 0BU  
UNITED KINGDOM

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# PRODUCT INFORMATION LEAFLET

## 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.

- 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.

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)

#### 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 allergies)
- 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 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.

#### 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.

### 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 (E 171), yellow iron oxide (E 172).

Film-coating 20 mg 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

**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 and Manufacturer

Marketing Authorisation Holder

Glenmark Generics (Europe) Ltd  
Laxmi House, 2 B Draycott Avenue,  
Kenton, Middlesex, HA3 0BU, United Kingdom

Manufacturer

Actavis hf. Reykjavikurvegur 78, IS-220  
Hafnarfjörður, Iceland

*And/or*

Actavis Ltd, BLB016 Bulebel Industrial Estate,  
Zejtun ZTN 3000, Malta

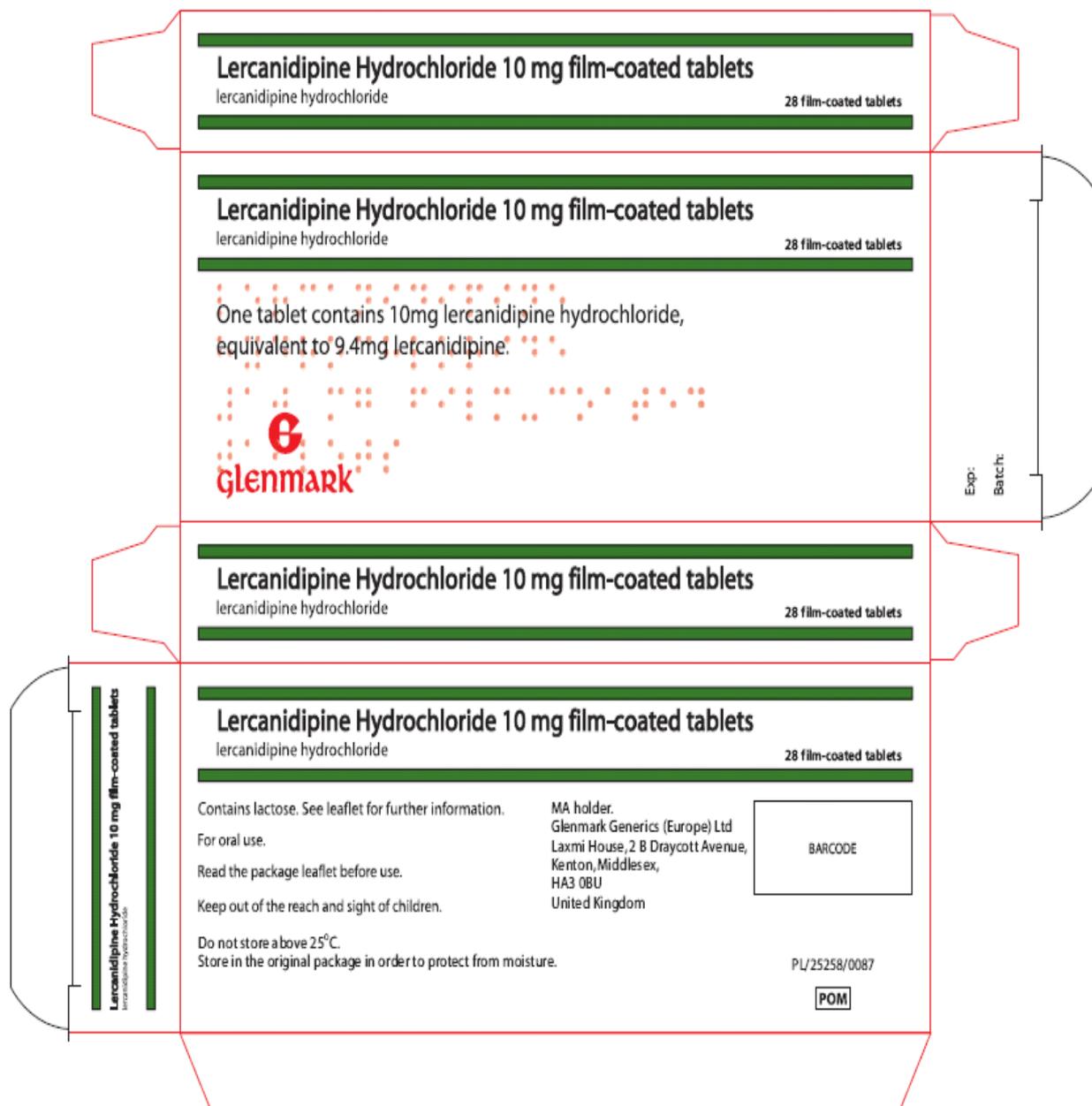
*And/or*

Balkanpharma - Dupnitsa AD, 3 Samokovsko  
Schosse Str., Dupnitsa 2600, Bulgaria

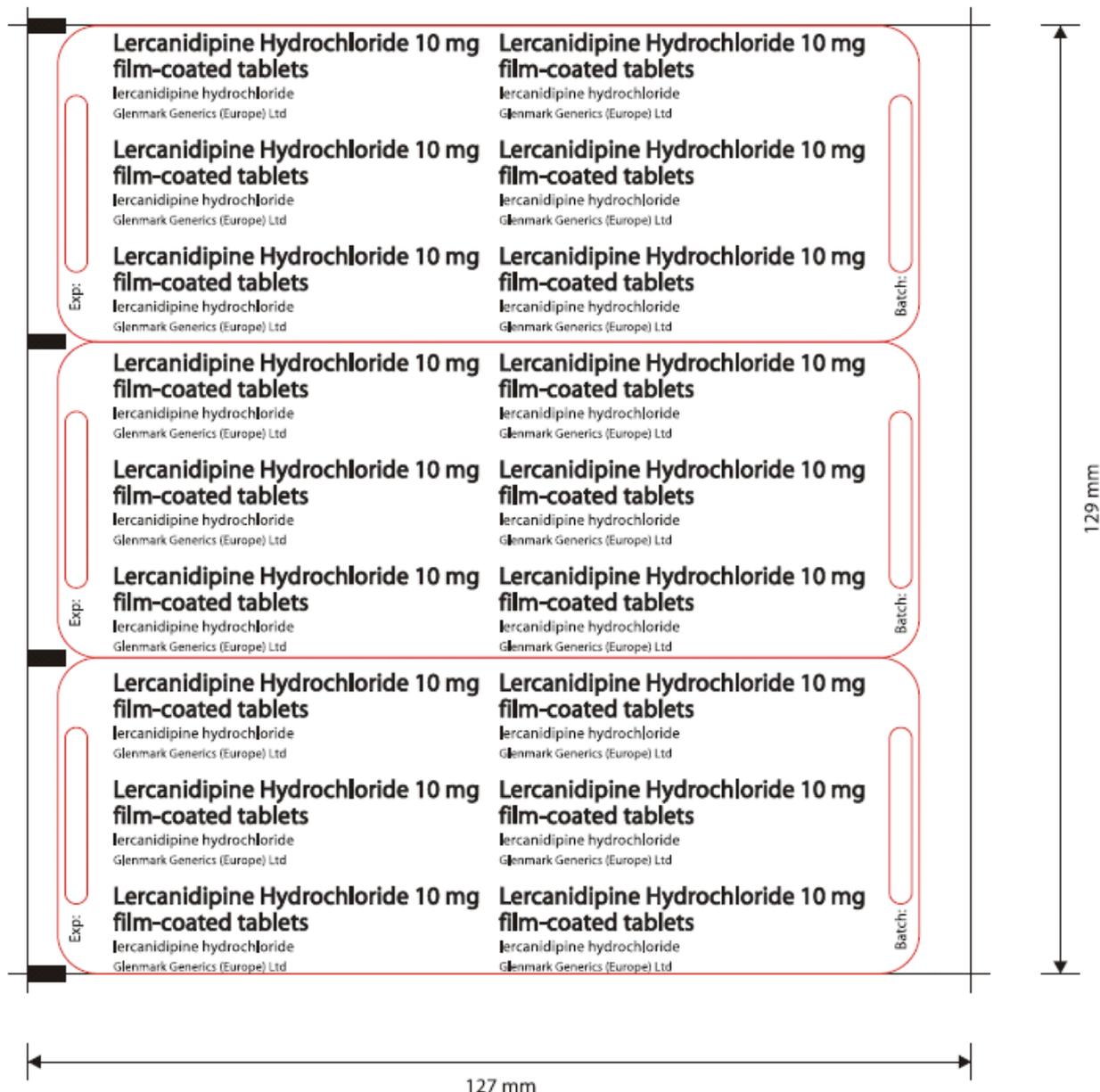
**This Leaflet was last approved in July 2010**

# LABELLING

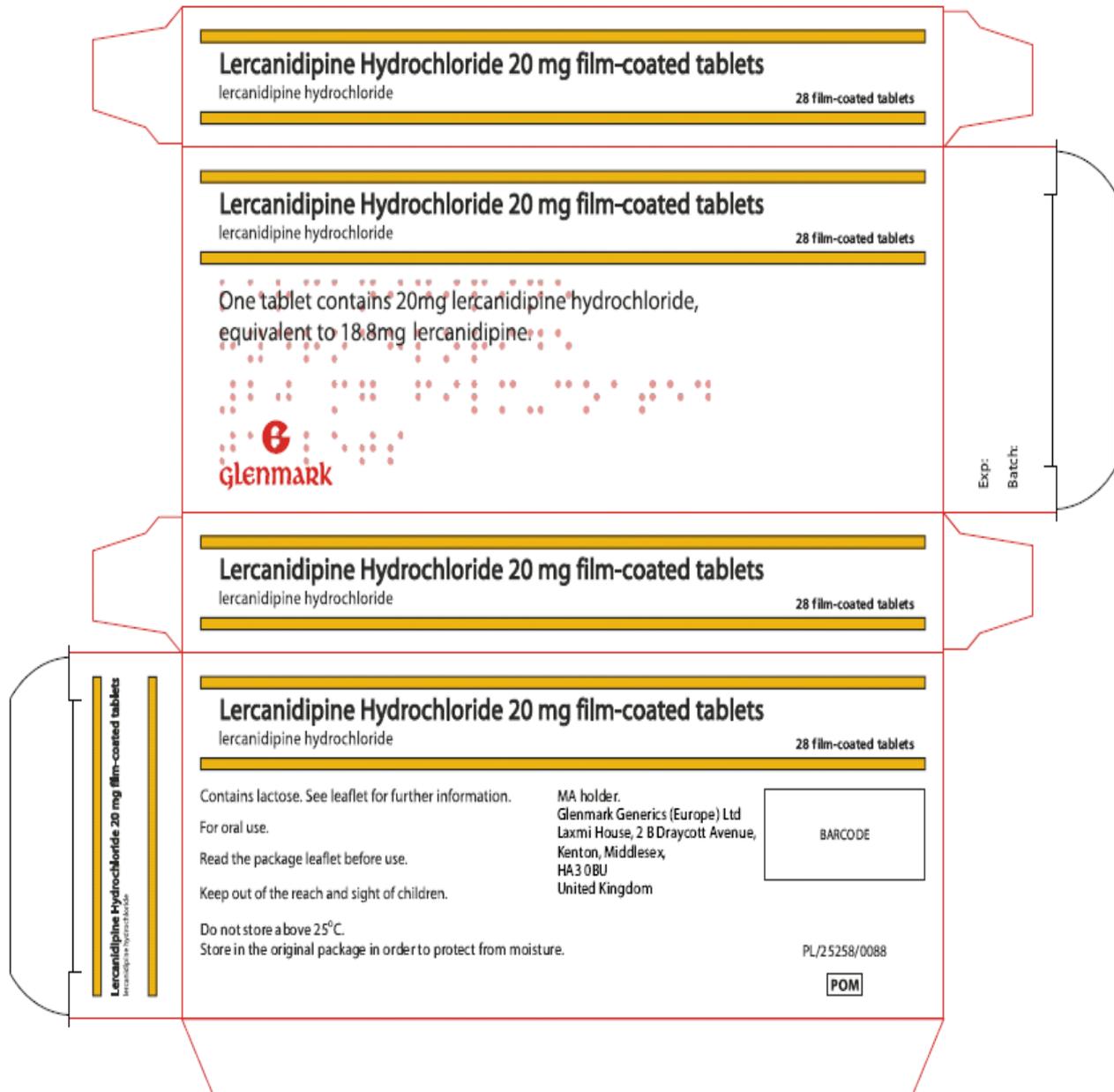
## Carton:



**Blister:**



**Carton:**



**Blister:**

