LERCAPRESS 10 mg/10 mg, film-coated tablets
Pack of 30 (CIP code: 385 953-3)
Pack of 90 (CIP code: 387 387-5)

Applicant: PIERRE FABRE MEDICAMENT

Enalapril/Lercanidipine

List I

Date of Marketing Authorisation: 09/07/2008 (MA variation of 01/08/2008)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals.
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

LERCAPRESS 10 mg / 10 mg: 1 tablet contains 10 mg of enalapril maleate (equivalent to 7.64 mg of enalapril) and 10 mg of lercanidipine hydrochloride (equivalent to 9.44 mg of lercanidipine).

NB: This is the first fixed-dose combination of enalapril and lercanidipine.

1.2. Indication

- LERCAPRESS 10 mg / 10 mg: “Treatment of essential hypertension in patients insufficiently controlled by the administration of lercanidipine 10 mg as monotherapy. LERCAPRESS 10 mg/10 mg fixed-dose combination should not be used for initial treatment of hypertension”.

1.3. Dosage

LERCAPRESS 10 mg / 10 mg: “In hypertensive patients insufficiently controlled by lercanidipine 10 mg monotherapy, the dose of lercanidipine may be increased to 20 mg as monotherapy or treatment may be replaced by LERCAPRESS 10 mg /10 mg”.

Individual dosage adjustment of each ingredient is recommended. A direct switch from monotherapy to the fixed-dose combination may be attempted if clinically justified.

The usual recommended dosage is one tablet per day administered at least 15 minutes before meals. Treatment should preferably be administered in the morning. This medicinal product must not be taken with grapefruit.

Specific situations
- Elderly patients: The dosage must be adjusted according to renal function (see “Use in patients with impaired renal function”).
- Children and adolescents aged under 18 years: the use of LERCAPRESS is not currently recommended as there are no clinical data.
- Renal impairment: LERCAPRESS is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min) or in patients on haemodialysis. Treatment must be instituted with caution in patients with mild to moderate renal impairment.
- Hepatic impairment: LERCAPRESS is contra-indicated in patients with severe impairment of hepatic function. Treatment must be instituted with caution in patients with mild to moderate hepatic impairment.
2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

C : Cardiovascular system
C09 : Medicinal products acting on the renin-angiotensin system
C09B : Angiotensin-converting enzyme inhibitors (ACEi) in combination
C09BB : Angiotensin-converting enzyme inhibitors (ACEi) and calcium antagonists.
C09BB02 : Enalapril and lercanidipine

2.2. Medicines in the same therapeutic category

- Separate administration of 10 mg/day of enalapril (RENITEC 5 mg or 20 mg, tablets) and 10 mg/day of lercanidipine (LERCAN 10 mg, ZANIDIP 10 mg, tablets).

- Fixed-dose combinations of an ACEi and a calcium channel blocker: trandolapril 2 mg + verapamil 180 mg; TARKA PR; OKADRIK PR.

2.3. Medicines with a similar therapeutic aim

All medicinal products indicated in the treatment of essential hypertension: other antihypertensives prescribed as monotherapy or in combinations.

Other medicines containing fixed-dose combinations of an ACEi, calcium channel blocker or sartan:

a. Angiotensin-II receptor antagonist (sartans) + calcium channel blocker:
valsartan 80 mg/160 mg + amlodipine 5 mg/10 mg: EXFORGE

b. ACEi + Diuretic:
benazepril 10mg + HCTZ\textsuperscript{1} 12.5mg: BRIAIZE, CIBADREX
captopril 50mg + HCTZ 25.0mg: CAPTEA, ECAZIDE, and G\textsuperscript{2}
enalapril 20mg + HCTZ 12.5mg: CO-RENETEC, and G
fosinopril 20mg + HCTZ 12.5mg: FOZIRETIC
lisinopril 20mg + HCTZ 12.5mg: PRINZIDE, ZESTORETIC, and G
perindopril 2 mg (4mg) + indapamide 0.625 mg (1.25mg): PRETERAX, BIPRETERAX
quinapril 20mg + HCTZ 12.5mg: ACUILIX, KORETIC, and G
ramipril 5 mg + HCTZ 12.5 mg: COTRIATEC
zofenopril 30 mg + HCTZ 12.5 mg: ZOFENILDUO

c. Angiotensin-II receptor antagonists (sartans) + Diuretic:
candesartan 8 mg or 16 mg + HCTZ 12.5 mg: COKENZEN, HYTACAND
eprosartan 600 mg + HCTZ 12.5 mg: COTEVETEN
irbesartan 150 mg (or 300 mg) + HCTZ 12.5 mg (or 25 mg) COAPROVEL
losartan 50 mg (or 100 mg) + HCTZ 12.5 mg (or 25 mg) FORTZAAR, HYZAAR
olmesartan medoximil 20 mg + HCTZ 12.5 mg (or 25 mg) ALTEISDUO, COOLMETEC
telmisartan 40 mg or 80 mg + HCTZ 12.5 mg MICARDISPLUS, PRITORPLUS
valsartan 80 mg or 160 mg + HCTZ 12.5 mg (or 25 mg) COTAREG, NISISCO

d. Calcium channel blocker + beta-blocker:
nifedipine 20 mg + atenolol 50 mg: BETA-ADALATE, TENORDATE, and G

\textsuperscript{1} Hydrochlorothiazide, thiazide diuretic: “HCTZ”.
\textsuperscript{2} “G”: proprietary generic medicines. Cf. list of generic drugs, Afssaps.

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3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The evaluation of the efficacy and adverse effects of LERCAPRESS is mainly based on the results of a comparative study: study CPL1-0018.

Design
The objective of this randomised, double-blind, parallel-group study was to show that the enalapril 10 mg (E10) + lercanidipine 10 mg (E10/L10) combination has an additional antihypertensive efficacy in hypertensive patients insufficiently controlled by lercanidipine monotherapy 10 mg (L10).
An open-label follow-up phase of nine months was added.

The primary endpoint (efficacy) was the mean reduction in seated diastolic blood pressure (DBP) between the two arms, after 12 weeks (3 months) of treatment, in the ITT population. Baseline values were the measurements made after 4 weeks of lercanidipine monotherapy.

**NB:** For an expected reduction of 3 mm Hg in DBP, a sample of 272 patients (136 per arm) was necessary to obtain a power of 90% with a two-sided significance level \( \alpha = 0.05 \). A total of 300 patients therefore had to be included assuming that 10% of patients are lost to follow-up.

Secondary efficacy endpoints were in particular:
- Mean reduction in the seated systolic blood pressure (SBP);
- Percentage of patients with "normal" blood pressure at the end of the study according to the following criteria:
  - Percentage of patients with DBP < 90 mm Hg
  - Percentage of patients with SBP < 140 mm Hg
  - Percentage of patients with BP < 140/90 mm Hg
- Percentage of "responder" patients with the following values:
  - DBP < 90 mm Hg or reduction compared to baseline values \( \geq 10 \) mm Hg
  - SBP < 140 mm Hg or reduction compared to baseline values \( \geq 20 \) mm Hg

Main inclusion criteria:
- Man or woman aged at least 18 years;
- Diagnosis of essential hypertension;
- No significant sign of disease other than hypertension, in the investigator's opinion;

Main exclusion criteria:
- Secondary hypertension;
- Heart failure (New York Heart Association, (NYHA) class III and IV);
- Valvular heart disease; cardiac arrhythmia;
- Hypertensive retinopathy;
- Diabetes mellitus with poor blood glucose control or diabetes mellitus complicated by retinopathy, peripheral neuropathy or clinically significant autonomic neuropathy;
- Serum creatinine > 1.5 times upper limit of normal (ULN); hepatic enzymes > 2 times ULN (aspartate aminotransferase ASAT and/or alanine aminotransferase ALAT); serum bilirubin > 1.5 times ULN.
- Patients weighing more than 40% of their ideal weight for their height according to the Broca index: height (in centimetres) - 100 = ideal body weight (in kg);
- Non-compliance during the single-blind screening period, defined as taking less than 80% or more than 120% of the assigned study medication.
NB: during the screening periods on placebo and the single-blind monotherapy periods, patients with DBP > 114 mm Hg or SBP > 189 mm Hg were withdrawn from the study (for safety reasons). Patients with a DBP < 95 mm Hg were considered “responders” to treatment and were therefore also withdrawn. From visit 5 until the end of the study, patients with a DBP > 109 mm Hg or SBP > 179 mm Hg were withdrawn from the study (for safety reasons).

Results

This study was performed in 342 patients insufficiently controlled by 10 mg of lercanidipine, i.e. with a diastolic blood pressure between 95 and 114 mm Hg and a systolic blood pressure between 140 and 189 mm Hg.

Primary efficacy endpoint: the reduction in diastolic blood pressure was - 7.1 mm Hg in the E10/L10 arm versus - 4.3 mm Hg in the L10 arm, i.e. an additional reduction in favour of the combination of 2.8 mm Hg, p<0.001.

Secondary endpoints:
- An additional reduction in the systolic blood pressure of 5.4 mm Hg (p<0.001) in favour of the combination was observed.
- The responder rate was higher with the fixed-dose combination than with monotherapy: 41% versus 24% (p<0.001) for the systolic blood pressure and 35% versus 24%, (p=0.032) for the diastolic blood pressure.
- Normal blood pressure values were restored in a higher percentage of patients receiving the fixed-dose combination (29% versus 19%, p=0.023, and 39% versus 22%, p<0.001 for DBP and SBP respectively) than in those on monotherapy.

Mean DBP and SBP values after 12 weeks of treatment:

<table>
<thead>
<tr>
<th></th>
<th>L10/E10</th>
<th>L10</th>
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<tbody>
<tr>
<td>n=167</td>
<td></td>
<td>n=175</td>
</tr>
<tr>
<td>Mean baseline DBP (mm Hg)</td>
<td>100 +/- 3</td>
<td>100 +/- 4</td>
</tr>
<tr>
<td>Mean baseline SBP (mm Hg)</td>
<td>152 +/- 11</td>
<td>152 +/- 11</td>
</tr>
<tr>
<td>Mean change from baseline in DBP (mm Hg/95% CI) after 12 weeks.</td>
<td>-7.1 +/- 0.63</td>
<td>-4.3 +/- 0.62</td>
</tr>
<tr>
<td>Mean change from baseline in SBP (mm Hg/95% CI) after 12 weeks.</td>
<td>-7.7 +/- 1.05</td>
<td>-2.3 +/- 1.03</td>
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</table>

Remarks: The results of this study have little clinical relevance for the assessment of the benefit of LERCAPRESS 10 mg /10 mg in the management of hypertensive patients. The antihypertensive efficacy was assessed by comparison with lercanidipine monotherapy at a dosage of 10 mg/day in patients already considered to be insufficiently controlled by 10 mg/day of lercanidipine. Moreover, in routine practice, the dosage of enalapril required to obtain blood pressure control is 20 mg/day in most patients and not 10 mg/day.
3.2. Adverse effects

The study data showed that the combination of these two active ingredients did not cause any new adverse effects.

In the safety analysis of all the studies in the MA dossier, treatment-related adverse events were observed in 39/329 (11.9%) of patients with E10/L10 and in 69/410 (16.8%) of patients with E20/L10. The most frequent adverse effects during these studies were cough (5.6%), nausea (2.5%) and headaches (2.1%).

3.3. Conclusion

LERCAPRESS is a fixed-dose combination of enalapril and lercanidipine. Its clinical evaluation was mainly based on the results of a randomised double-blind comparison of an "add-on" treatment in 342 patients insufficiently controlled by 10 mg of lercanidipine. An additional reduction of 2.8 mm Hg in the diastolic blood pressure was obtained with the combination of 10 mg of lercanidipine + 10 mg of enalapril (-7.1 mm Hg versus -4.3 mm Hg, p<0.001) compared to treatment with 10 mg/day of lercanidipine for 12 weeks.

This study shows that the combination of these two antihypertensives (lercanidipine + enalapril) reduces blood pressure values more effectively than one of these agents used alone (lercanidipine 10 mg).

The value of using these two antihypertensives in a fixed-dose combination compared with separate administration was not established.

Moreover, the combination of 10 mg of lercanidipine and 10 mg of enalapril was not shown to have any benefit in terms of a reduction in morbidity and mortality.

The usefulness of this combination compared to other antihypertensive combinations (medicinal products in the same class or other classes) was not shown.

The safety profile of the lercanidipine 10 mg + enalapril 10 mg combination during studies was the same as that known for the two active ingredients. A reduction in the risk of adverse effects with the low-dose combination (10 mg/10 mg) was not therefore established.
4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Essential hypertension may have life-threatening complications. These proprietary drugs are intended for preventive treatment.

The efficacy/safety ratio of LERCAPRESS 10 mg/10 mg combination, evaluated from the reduction in blood pressure values, is moderate.

The therapeutic value of LERCAPRESS 10 mg/10 mg was not clearly established as it was assessed from the results of a clinical study comparing the antihypertensive efficacy of 10 mg/day enalapril + 10 mg/day of lercanidipine with that of 10 mg/day of enalapril in patients already insufficiently controlled by 10 mg/day of enalapril. The relevance of this study for the assessment of the clinical value of LERCAPRESS 10 mg/10 mg in the management of hypertensive patients may be doubted as monotherapy with 10 mg/day enalapril was unable to control blood pressure in most of these patients. No assessment was made of this fixed-dose combination compared to enalapril monotherapy at the usual dose (20 mg/day), other monotherapies (many alternatives are available) or other antihypertensive combinations with better-established efficacy (cf. ACCOMPLISH3 study results for example where the protocol planned to treat patients at maximum tolerated doses). The population of the patients who may benefit from this combination is not defined (cf. target population).

Public health benefit
The public health burden of essential hypertension and the cardiovascular diseases for which hypertension is a risk factor is high. A reduction in the morbidity and mortality caused by hypertension is a recognised public health need (priority identified by GTNDO* and the law of public health). However, existing treatments (including the free combination of Enalapril and Lercanidipine) already help address this need. There is no evidence suggesting that treatment by this fixed-dose combination is better that a free combination of these two active ingredients (including in terms of compliance). The proprietary medicine LERCAPRESS is not therefore expected to have an impact on morbidity and mortality or quality of life. Accordingly, the proprietary drug LERCAPRESS is not expected to benefit public health.


There are many alternative medications with a demonstrated benefit in terms of a reduction in morbidity and mortality: diuretics, beta-blockers, calcium channel blockers (including amlodipine) or other renin-angiotensin system antagonists.

Conclusion: The actual benefit of LERCAPRESS 10 mg/10 mg is insufficient in view of the available clinical data: this data is insufficient to assess its value for the management of hypertensive patients.

4.2. Improvement in actual benefit

Not applicable

4.3. Therapeutic use

Antihypertensive medication aims to prevent the cardiovascular and renal complications of hypertension. The objective of these agents is to restore normal blood pressure values. Diuretics, beta-blockers, calcium channel blockers and other renin-angiotensin system antagonists have been shown to reduce the occurrence of cardiovascular complications. For these reasons, the national or international recommendations propose to start antihypertensive treatment with one of these medicinal products.

The Committee points out that the value of fixed-dose combinations in the management of hypertensive patients in comparison with separate administration of (two) drugs has not been established.

4.4. Target population

Not applicable

4.5. Transparency Committee recommendations

The Transparency Committee did not recommend inclusion of LERCAPRESS 10 mg/10 mg on the list of medicines reimbursed by National Insurance and on the list of medicinal products approved for use in the hospital and various public services in the indications and dosages of the MA.