ZANEXTRA 20 mg/10 mg film-coated tablets
Package of 30 tablets (CIP: 385 967.4)
Package of 90 tablets (CIP: 387 392.9)

Applicant: BOUCHARA RECORDATI

Enalapril/Lercanidipine

List I

Date of Marketing Authorisation: 09/07/2008 (revised on 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

ZANEXTRA 20 mg/10 mg: 1 tablet contains 20 mg of enalapril maleate (equivalent to 15.29 mg of enalapril) and 10 mg of lercanidipine hydrochloride (equivalent to 9.44 mg of lercanidipine).

N.B.: This is the first fixed combination of enalapril and lercanidipine.

1.2. Indication

ZANEXTRA 20 mg/10 mg: Treatment of essential hypertension in patients inadequately controlled by enalapril 20 mg monotherapy.

The fixed combination ZANEXTRA 20 mg/10 mg is not to be used as the initial form of treatment for hypertension.

1.3. Dosage

ZANEXTRA 20 mg/10 mg: in patients whose blood pressure is inadequately controlled by enalapril 20 mg monotherapy, the dosage of enalapril may be increased in monotherapy or the enalapril may be replaced with ZANEXTRA 20 mg/10 mg.

- It is recommended that the dosage of each component be adjusted individually. A change from monotherapy directly to the fixed combination may be considered if it is clinically justifiable.
- The recommended standard dosage is one tablet daily to be taken at least 15 minutes before food. Treatment should be given preferably in the morning. This medicinal product must not be taken together with grapefruit.

Specific situations
- Elderly patients: The dosage should be adjusted according to the patient's renal function (see 'Use in cases of renal impairment').
- Children and adolescents under the age of 18 years: Use of ZANEXTRA is currently not recommended due to the lack of clinical data.
- In cases of renal impairment: ZANEXTRA is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min) or in patients requiring dialysis. Treatment should be initiated with caution in patients with mild to moderate renal impairment.
- In cases of hepatic impairment: ZANEXTRA is contraindicated in cases of severe hepatic impairment. Treatment should be initiated with caution in patients with mild to moderate hepatic impairment.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

C : Cardiovascular system
C09 : Agents acting on the renin-angiotensin system
C09B : ACE inhibitors, combinations
C09BB : ACE inhibitors and calcium channel blockers
C09BB02 : enalapril and lercanidipine
2.2. Medicines in the same therapeutic category

- Enalapril 20 mg daily (RENITEC 20 mg, tablets) and lercanidipine 10 mg daily (LERCAN 10 mg, ZANDIP 10 mg, tablets) taken separately.
- Fixed-dose combinations of an ACE inhibitor and a calcium channel blocker: trandolapril 2 mg + verapamil 180 mg: TARKA LP; OKADRIK LP.

2.3. Medicines with a similar therapeutic aim

All medicinal products indicated for the treatment of essential hypertension: other antihypertensive agents prescribed as monotherapy or in combination.

Other proprietary products based on a fixed-dose combination of an ACE inhibitor, calcium channel blocker or sartan:

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

b. ACE inhibitor + diuretic:
benazepril 10 mg + HCTZ¹ 12.5 mg: BIAZIDE, CIBADREX
captopril 50 mg + HCTZ 25.0 mg: CAPTEA, ECAZIDE, and G²
enalapril 20 mg + HCTZ 12.5 mg: CO-RENITEC, and G
fosinopril 20 mg + HCTZ 12.5 mg: FOZIRETIC
lisinopril 20 mg + HCTZ 12.5 mg: PRINZIDE, ZESTORETIC, and G
perindopril 2 mg (4 mg) + indapamide 0.625 mg (1.25 mg): PRETERAX, BIPRETERAX
quinapril 20 mg + HCTZ 12.5 mg: 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 medoxomil 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

¹ HCTZ – Hydrochlorothiazide, a thiazide diuretic.
² G – Generic medicinal products. See the AFSSAPS list of generics.
3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy and adverse effects of ZANEXTRA 20 mg/10 mg can be assessed mainly from the results of a comparative study: study CPL1-0019.

Methodology

It was a randomised, double-blind, parallel-group study with the aim of demonstrating that the combination of enalapril 20 mg + lercanidipine 10 mg (E20/L10) provides additional antihypertensive efficacy in hypertensive patients inadequately controlled by enalapril 20 mg monotherapy (E20).

A nine-month open-label extension phase was added to each of these two studies.

The primary endpoint (efficacy) was the mean reduction in sitting diastolic blood pressure (SDBP) between the two arms of the ITT population after 12 weeks (3 months) of treatment. The baseline values were measurements taken after the 6-week period of enalapril monotherapy.

\[ \text{N.B.} \quad \text{For an expected SDBP reduction of 3 mmHg, with a power of 90\% and a two-tail 5\% \( \alpha \) risk, a sample of 272 patients (136 per arm) was required. A total of 300 patients was planned for inclusion, since it was considered that 10\% of patients would drop out.} \]

Secondary efficacy endpoints were particularly:
- Mean reduction in sitting systolic blood pressure (SSBP);
- Percentage of ‘normalised’ patients at the end of the study on the following criteria:
  - Percentage of patients with SDBP < 90 mmHg
  - Percentage of patients with SSBP < 140 mmHg
  - Percentage of patients with BP < 140/90 mmHg
- Percentage of responders with the following results:
  - SDBP < 90 mmHg or reduction from baseline \( \geq \) 10 mmHg
  - SSBP < 140 mmHg or reduction from baseline \( \geq \) 20 mmHg.

Inclusion criteria, particularly:
- Male or female at least 18 years of age;
- Diagnosis of essential hypertension;
- No sign of significant disease other than hypertension, in the investigator’s opinion.

Exclusion criteria, particularly:
- Secondary hypertension;
- Heart failure (New York Heart Association – NYHA classes III and IV);
- Heart valve disease; cardiac arrhythmia;
- Hypertensive retinopathy;
- Diabetes mellitus with poor blood glucose control or complicated diabetes mellitus with retinopathy, peripheral neuropathy or clinically significant autonomous neuropathy.
- Serum creatinine > 1.5 times the upper limit of normal (ULN); liver enzymes > 2 times the ULN (aspartate aminotransferase ASAT and/or alanine aminotransferase ALAT); serum bilirubin > 1.5 times the ULN;
- Patients weighing 40\% more than the ideal weight for their height according to Broca’s formula: height (in centimetres) - 100 = ideal body weight (in kg);
- Non-compliance during the single-blind run-in phase, defined as taking less than 80\% or more than 120\% of the assigned study drug.
NB: During the placebo run-in period and the single-blind monotherapy periods, patients with SDBP > 114 mmHg or SSBP > 189 mmHg were taken out of the study (for safety reasons). Patients with SDBP < 95 mmHg were also removed, as they were responding to the treatment. From visit 5 to the end of the study, patients with SDBP > 109 mmHg or SSBP > 179 mmHg were taken out of the study (for safety reasons).

Results

This study was performed on 327 patients inadequately controlled by enalapril 20 mg who had a diastolic blood pressure of 95-114 mmHg and a systolic blood pressure of 140-189 mmHg.

Primary endpoint: the reduction in sitting diastolic blood pressure was -9.2 mmHg in the E20/L10 arm versus -7.5 mmHg in the E20 arm, or an additional reduction of 1.8 mmHg, p=0.015, in favour of the combination.

Secondary endpoints:
- The proportion of responders to the fixed combination was not significantly different from the proportion responding to the monotherapy: 53% versus 43% (p=0.076) for SDBP and 41% versus 33% (p=0.116) for SSBP.
- The percentage of patients taking the E20/L10 fixed combination who had normalised diastolic blood pressure (48% versus 37%, p=0.055) or normalised systolic blood pressure (33% versus 28%, p=0.325) was not different from the percentage of E20 monotherapy patients.

Mean SDBP and SSBP after 12 weeks of treatment:

<table>
<thead>
<tr>
<th></th>
<th>L10/E20 n=163</th>
<th>E20 n=164</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline SDBP (mmHg)</td>
<td>99 +/- 4</td>
<td>99 +/- 4</td>
</tr>
<tr>
<td>Mean baseline SSBP (mmHg)</td>
<td>154 +/- 11</td>
<td>154 +/- 11</td>
</tr>
<tr>
<td>Mean change in SDBP (mmHg/95%CI) after 12 weeks</td>
<td>-9.2 +/- 0.64</td>
<td>-7.5 +/- 0.64</td>
</tr>
<tr>
<td>Mean change in SSBP (mmHg/95%CI) after 12 weeks</td>
<td>-9.8 +/- 1.11</td>
<td>-6.7 +/- 1.11</td>
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</tbody>
</table>

Remark: The results of this study are of limited clinical relevance for judging the benefit of ZANEXTRA 20 mg/10 mg in the treatment of hypertensive patients. In fact, its antihypertensive efficacy was appraised in comparison with enalapril 20 mg daily monotherapy in patients already considered inadequately controlled by enalapril 20 mg daily.

Other data:

Study IT-CL 0044 was performed specifically on patients aged at least 60 years. It was a 16-week, randomised, double-blind, placebo-controlled, sequential design study with 4 arms: placebo, lercanidipine 10 mg (L10), enalapril 20 mg (E20), and enalapril 20 mg plus lercanidipine 10 mg combination (E20/L10). There were four 4-week periods in which each patient tested each of the four treatments successively in randomised order (crossover trial). Its aim was to assess whether the E20/L10 combination was more effective than either of the medicinal products taken separately in reducing systolic blood pressure in patients aged at least 60 years.

- Hypertensive patients aged 60-80 years with office sitting systolic blood pressure (SSBP) of 160-179 mmHg (inclusive), sitting diastolic blood pressure (SDBP) < 110 mmHg and mean daytime systolic blood pressure (SBP) ≥ 135 mmHg were included in the study. High-risk patients – patients with severe hypertension, a history of cardio- or cerebrovascular complications or diabetes mellitus requiring drug treatment – were not included. Patient baseline characteristics did not differ.
The primary efficacy endpoint was mean 24-hour SBP, measured by an ambulatory blood pressure monitoring (ABPM) device at the end of 4 weeks of treatment for each medication.

- Results: In the per protocol population (62 patients), all the active medications reduced ambulatory and office systolic and diastolic blood pressures compared with placebo, but the E20/L10 combination therapy showed significantly greater efficacy than the enalapril or lercanidipine monotherapies. The short duration of this study and the limited number of patients assessed make it impossible to draw any conclusion.

### 3.2. Adverse effects

The study data showed that the combination of these two active substances did not lead to the appearance of new undesirable effects.

In the safety analysis of all the studies submitted in the marketing authorisation dossier, adverse events attributable to the treatments were observed in 39/329 (11.9%) patients taking E10/L10 and in 69/410 (16.8%) patients taking E20/L10. The most common adverse effects reported in these studies were cough (5.6%), nausea (2.5%) and headache (2.1%).

### 3.3. Conclusion

ZANEXTRA is a fixed-dose combination of enalapril and lercanidipine. Clinical evaluation of ZANEXTRA relies mainly on the results of a randomised, double-blind comparative study of add-on treatment performed on 327 patients inadequately controlled by enalapril 20 mg. The reduction in diastolic blood pressure was -9.2 mmHg in the group treated with the enalapril 20 mg + lercanidipine 10 mg combination versus -7.5 mmHg in the group treated with enalapril 20 mg (p=0.015). This study shows that the combination of these two antihypertensive agents (lercanidipine + enalapril) is more effective at reducing blood pressure than one of them (enalapril 20 mg) alone.

The benefit of giving these two antihypertensive agents in a fixed-dose combination rather than separately has not been established. In addition, the impact of the combination of lercanidipine 10 mg and enalapril 20 mg in terms of reducing morbidity and mortality has not been established. The benefit of this combination compared with that of other combinations of antihypertensive agents (in the same or different classes) has not been documented.

The safety profile of the lercanidipine 10 mg + enalapril 20 mg combination was not different from the known profiles of the two active substances.
4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Essential hypertension may be life threatening because of its complications. These medicinal products may be classed as preventive medicines.

The efficacy/adverse effects ratio of ZANEXTRA 20 mg/10 mg in reducing blood pressure is high.

ZANEXTRA 20 mg/10 mg is a second-line medicine for patients whose blood pressure is inadequately controlled by enalapril 20 mg daily or by lercanidipine 10 mg daily after 12 weeks of treatment. This combination has not shown any impact in terms of reducing morbidity or mortality.

Public health benefit
Essential hypertension and the cardiovascular diseases for which it is a risk factor represent a substantial public health burden. Reducing the morbidity and mortality attributable to hypertension is a public health need (a priority identified by the GTNDO and the Public Health Act). However, existing treatments (including the free combination of enalapril and lercanidipine) already contribute to meeting this need.
There is no argument to suggest there is any advantage in treating patients with this fixed combination rather than with a free combination of these two active substances (including in terms of compliance). ZANEXTRA is therefore not expected to have an impact on morbidity/mortality or quality of life. Consequently, the proprietary product ZANEXTRA is not expected to benefit public health.


There are many alternative pharmaceutical products that have shown an impact in terms of morbidity/mortality: diuretics, beta-blockers, calcium channel blockers (such as amlodipine) or other renin-angiotensin system antagonists.

Conclusion: the actual benefit of ZANEXTRA 20 mg/10 mg is substantial.

4.2. Improvement in actual benefit

The proprietary product ZANEXTRA 20 mg/10 mg, a fixed-dose combination of enalapril maleate 20 mg and lercanidipine hydrochloride 10 mg, does not provide any improvement in actual benefit (IAB level V) compared with the joint use of each of its components taken separately.

4.3. Therapeutic use

The purpose of antihypertensive treatment is to prevent the cardiovascular and renal complications of hypertension. Treatment should seek to normalise blood pressure. Diuretics, beta-blockers, calcium channel blockers and renin-angiotensin system antagonists have demonstrated their ability to reduce the occurrence of cardiovascular complications. National and international guidelines therefore propose that antihypertensive treatment should be initiated with one of these medicinal products.

ZANEXTRA 20 mg/10 mg is a second-line medicine that should only be prescribed for patients who have already been treated and brought under control with enalapril 20 mg daily and lercanidipine 10 mg daily.
The Committee notes that the benefit of a fixed-dose combination in the treatment of hypertensive patients compared with the two medicines taken separately has not been established.

4.4. Target population

The prevalence of diagnosed and/or treated hypertension is about of 6.5-7.4 million patients (HCSP 2002 and CREDES 1999 data extrapolated to the population of France in 2003, THALES/CEMKA 2001).

However, the true prevalence of hypertension may be higher than that of diagnosed and/or treated hypertension. The MONICA survey has in fact shown that only 52.2% of hypertensive individuals aged between 35 and 64 were aware of their hypertension.

If we extrapolate from the MONICA data and assume that only 52.2% of patients with hypertension are actually diagnosed and/or treated, the true prevalence of hypertension might be in the order of 12.5-14.2 million people.

By way of information, a study on the ways in which hypertension is treated in general medicine (THALES/CEMKA 2001) shows that:

- 49% of patients are treated with monotherapy, 34% with bitherapy, 13% with tritherapy and 4% with quadritherapy or more;
- 31% of patients are treated with beta-blockers, 27% with ACE inhibitors (alone or in combination), and 26% with calcium channel blockers.

There is no available data to estimate the percentage of patients in France treated with enalapril 20 mg daily and lercanidipine 10 mg daily whose blood pressure is under control. The target population for ZANEXTRA 20 mg/10 mg cannot be calculated.

By way of an example, of the 3,260,000 members of the RSI (insurance scheme for the self-employed), approximately 1,200 are treated with enalapril 20 mg daily and lercanidipine 10 mg daily (RSI usage data, October 2008).

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion of ZANEXTRA 20 mg/10 mg on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication and at the posology laid down in the marketing authorisation.

Packaging: packs of 30 and 90, appropriate to the prescription requirements.

Reimbursement rate: 65%.