



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

23 January 2008

ZANIDIP 10mg, film-coated tablets

B/28 (CIP: 347 638.7)

B/30 (CIP: 372 259.6)

B/90 (CIP: 372 260.4)

ZANIDIP 20mg, film-coated tablets

B/28 (CIP: 359 968.7)

B/30 (CIP: 372 286.3)

B/90 (CIP: 372 288.6)

Applicant : BOUCHARA RECORDATI

Lercanidipine hydrochloride

ATC code: C08CA13

List I

Dates of the Marketing Authorisations (MA) (National procedure):

- 10-mg dosage: 21 July 1998

- 20-mg dosage: 26 September 2002

Marketing Authorisation variation 8 January 2007 (adverse events section)

Reason for request: Reassessment of the IAB level.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Lercanidipine hydrochloride

1.2. Indication

Arterila hypertension

1.3. Dosage

This medicinal product is reserved for adults only.

For certain patients treatment can be initiated at a dose of 5 mg, and this dose may be sufficient.

The usual dose is 10 mg orally once a day.

The dose can be increased if necessary to 20 mg depending on the patient's individual response.

Another antihypertensive can be added if the patient's blood pressure is not adequately controlled.

Pharmacokinetic data and clinical experience indicate that there is no need to adjust dosage in elderly patients.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2006)

C: Cardiovascular system
C08: Calcium channel blockers
C08C: Selective calcium channel blockers with mainly vascular effects
C08CA: Dihydropyridine derivatives
C08CA13: Lercanidipine

2.2. Medicines in the same therapeutic category

2.2.1 Comparator medicinal products: calcium channel blockers in the dihydropyridine derivatives group (associations with other antihypertensives being excluded)

amlodipine : AMLOR 5 mg and AMLOR 10 mg, gelatin-coated capsules
felodipine : FLODIL LP 5 mg, tablets
isradipine : ICAZ LP 2.5 and ICAZ LP 5 mg, gelatin-coated capsules
lacidipine : CALDINE 2 mg and CALDINE 4 mg, tablets
lercanidipine : LERCAN 10 and LERCAN 20 mg, tablets
manidipine : IPERTEN 10 and IPERTEN 20 mg, tablets
nicardipine : LOXEN 20 mg, tablets and LOXEN LP 50 mg, gelatin-coated capsules
nifedipine : ADALATE LP 20, tablets
 CHRONADALATE LP 30 mg, tablets
nitrendipine : BAYPRESS 10 mg and BAYPRESS 20mg, tablets
 NIDREL 10 mg and NIDREL 20 mg, tablets

2.3. Medicines with a similar therapeutic aim

All drugs indicated for the treatment of arterial hypertension.

3 ANALYSIS OF AVAILABLE DATA

The manufacturer's request for a reassessment of the IAB is based on the results of the two clinical studies considered by the MA committee.

The manufacturer also submitted results of new data which are not discussed in this opinion because of their methodology: one "mechanistic" study¹ (with a non-clinical primary endpoint) and three "observational" studies^{2 3 4}.

3.1. Efficacy

Reminder:

- The aim of the double-blind COHORT study⁵ was to compare the tolerance profile of lercanidipine with that of two other calcium channel blockers, amlodipine and lacidipine, in hypertensive patients.

Eight hundred and twenty-eight (828) patients aged 60 and over were randomly assigned for treatment of mild to moderate arterial hypertension with lercanidipine 10 mg/day, amlodipine 5 mg/day or lacidipine 2 mg/day. The average duration of treatment was 12 months.

The proportion of patients with oedema of the lower limbs was 19% in the amlodipine group (n=200), 9.3% in the lercanidipine group (n=420) and 4.3% in the lacidipine group (n=208), p<0.0001.

The proportion of patients withdrawn from treatment because of peripheral oedema was 1.4% in the lacidipine group, 2.1% in the lercanidipine group and 8.5% in the amlodipine group (secondary criterion).

NB: The fall in blood pressure did not differ between the patients in these three groups.

- A randomised, double-blind study carried out in Norway⁶ compared the occurrence of peripheral oedema of the lower limbs (primary assessment criterion) in 92 hypertensive postmenopausal women treated with lercanidipine 10 mg/day or amlodipine 5 mg/day. After four weeks, the dosages were increased to 20 mg/day of lercanidipine and 10 mg/day of amlodipine. The lower limb oedema was assessed by the water displacement method using a volumetric boot for measurement on inclusion and after eight weeks of treatment.

The results presented related to 77 patients out of the 92 who were assigned at random to one of the treatment groups; the per-protocol analysis found the increase in leg volume to be smaller in the lercanidipine group (+ 5.3 ml compared to the value on inclusion) than in the amlodipine group (+60.4 ml compared to the value on inclusion), p<0.001.

NB: The fall in blood pressure did not differ between the patients in these two groups.

¹ Pedrinelli R, Dell'Omo G, Nuti M, Menegato A, Balbarini A, Mariani M. Heterogeneous effect of calcium antagonists on leg oedema: a comparison of amlodipine versus lercanidipine in hypertensive patients. *J Hypertens.* 2003 21(10):1969-73.

² Poncelet P, Ribstein J, Goullard L, Bassous M, Grès CS, Clerson P. Efficacy and acceptability of lercanidipine are not age dependent in patients with essential hypertension. the AGATE study. *Ann Cardiol Angeiol* 2004 53(3):123-30.

³ Barrios V, Navarro A, Esteras A et al. The ELYPSE Study. Antihypertensive efficacy and tolerability of lercanidipine in daily clinical practice.. *Blood Press* 2002;11(2):95-100.

⁴ Allaert FA, Scart-Gres C, Bassous M et al. Efficacité, tolérance et observance de ZANIDIP (lercanidipine) dans le traitement de l'hypertension artérielle essentielle en pratique quotidienne de médecine générale [Efficacy, tolerance and compliance of ZANIDIP (lercanidipine) in the treatment of essential hypertension in the routine practice of general medicine]. *Angéiologie* 2003;55(3) :1-8.

⁵ Leonetti G, Magnani B, Pessina AC, Rappelli A, Trimarco B, Zanchetti A. The COHORT Study Group. Tolerability of long-term treatment with lercanidipine *versus* amlodipine and lacidipine in elderly hypertensives. *Am J Hypertens.* 2002;15(11):932-40.

⁶ Lund-Johansen P, Strandén E, Helberg S et al. Quantification of leg oedema in postmenopausal hypertensive patients treated with lercanidipine or amlodipine. *J Hypertens.* 2003 21(5):1003-10.

3.2. Adverse events

Amendments were made to section 4.8 - Adverse events of the SPC for ZANIDIP in the light of a review of the results of these two studies by the MA committee (ZANIDIP ® 10 - 20 mg MA supplementation dated 8 January 2007).

"Adverse events are more likely to occur at the start of treatment or when the dose is being increased. They are generally benign and disappear when treatment is withdrawn: headaches, facial redness, sometimes accompanied by hot flushes, palpitations, oedema of the lower limbs. In the recent COHORT study, the proportion of lower limb oedemas observed in subjects monitored for 6 to 24 months was 9.3% in the lercanidipine group, 19.0% in the amlodipine group ($p < 0.0001$) and 4.3% in the lacidipine group. The fall in blood pressure was not significantly different in the three groups. In the recent study by Lund-Johansen, the proportion of lower limb oedemas observed was much lower ($p = 0.02$) in the lercanidipine group (9.1 %) than in the amlodipine group (28.6%). The fall in blood pressure was not significantly different in the two groups: $-21.9/9.5$ mmHg in the lercanidipine group vs. $-23.1/13.2$ mmHg in the amlodipine group".

Instances of dizziness were also reported.

- more rarely: fatigue, gastrointestinal disorders such as dyspepsia, nausea, vomiting, epigastric pain and diarrhoea; polyuria, skin rashes, drowsiness and myalgia.
- hypotension can occur in rare cases.
- gingival hyperplasia has been reported in rare cases following the use of other dihydropridines, although this was not observed during the clinical trials.
- like other vasoactive substances, lercanidipine can cause anginal pain at the start of treatment. If this occurs, treatments must be stopped.

3.3. Conclusion

The manufacturer's request to reassess the IAB for ZANIDIP compared to AMLOR is based on the results of two randomised clinical studies comparing the occurrence of adverse events at doses of 10-20 mg/day of lercanidipine to 5-10 mg/day of amlodipine in patients with arterial hypertension. In these studies, lercanidipine caused fewer cases of peripheral oedema than amlodipine after two months of treatment in one study (92 female patients) and after an average of 12 months and up to two years in the second study (828 patients).

The fall in blood pressure did not differ between the groups of patients. However, the committee emphasises that, unlike lercanidipine, amlodipine (AMLOR) has been found to have a positive impact on preventing complications associated with arterial hypertension. The level of evidence documenting the antihypertensive efficacy of amlodipine⁷ (AMLOR) is therefore higher than that available for lercanidipine (LERCAN/ZANIDIP).

⁷ Dahlöf B., Sever P., Poulter N et col. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the anglo Scandinavian cardiac outcomes trial-blood pressure lowering arm (ASCOTT-BPLA) : a multicentre randomized controlled trial. www.thelancet.com Vol. 366 September 10, 2005.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Arterial hypertension is a disease whose complications can affect the patient's vital prognosis.

These proprietary products come within the scope of preventive treatment.

The efficacy/safety ratio for lercanidipine is high.

ZANIDIP proprietary products are intended for first line treatment.

There are alternative drugs available.

The actual benefit of these medicinal products is substantial.

4.2. Reassessment of the improvement in actual benefit

In the light of all the clinical data available on morbidity, mortality and tolerance, the Transparency Committee is of the opinion that ZANIDIP does not offer any improvement in actual benefit (IAB V) over comparator drugs.

4.3. Therapeutic use

The aim of hypertension treatment is to prevent the cardiovascular and renal complications associated with hypertension. A normal blood pressure is targeted. Diuretics, betablockers, some calcium channel antagonists and renin-angiotensin system antagonists have been demonstrate their ability to reduce of reducing the occurrence of cardiovascular complications. This is why national and international recommendations advise practitioners to start hypertensive patients on one of these drugs.

Lercanidipine (ZANIDIP) is a calcium channel blocker that has not shown to have any effect on preventing hypertension complications.