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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

2 SYNOPSIS

Name of Sponsor: Menarini International Operations Luxembourg S.A.
Name of finished product: Olpress (Olmesartan medoxomil)
Name of active ingredient: Olmesartan medoxomil
Title of study: Efficacy and safety of olmesartan in elderly patients with mild to moderate hypertension
Protocol number: MEIN/03/OLM-HYP/001
EudraCT number: 2004-002077-23
Principal Investigator [redacted]
Study centre(s): n°49 involved, n° 31 enrolling patients
Publication (reference): ~~Not applicable~~ Blood Press.2011 Apr;1:3-11
Studied period (years): 2005-2009
Phase of development: Phase III
Objectives: The primary objective of the study was to assess the effectiveness of 12 weeks of double-blind treatment with olmesartan 10 to 40 mg once-daily in normalising sitting clinic diastolic blood pressure (DBP) as compared to ramipril 2.5 to 10 mg once-daily in elderly mild-moderate essential hypertensive patients. Secondary objectives of the study were: • The assessment of percentage of normalised (systolic or SBP<140 mmHg and DBP<90 mmHg for non-diabetic patients and SBP <130 mmHg and DBP <80 mmHg for diabetic patients) or responder patients (reduction in SBP ≥20 mmHg and of DBP ≥10 mmHg) after 2, 6 and 12 weeks of treatment with olmesartan as compared to ramipril • The effect of the two drugs on sitting clinic SBP and DBP changes with treatment (12 weeks) • The effect of the two drugs on sitting clinic pulse pressure (PBP), defined as the difference between SBP and DBP (12 weeks) • The assessment of the antihypertensive efficacy of the two drugs by ambulatory blood pressure monitoring (ABPM) during the 12-week double blind phase • Safety and tolerability of study drugs • Patient's compliance to treatment • The assessment of antihypertensive efficacy of 36 weeks of open label treatment with olmesartan 40 mg once-daily on clinic BP and ABP • The evaluation of long-term safety of olmesartan 40 mg once-daily
Methodology: **Trial design/type**: Multicentre, randomised, double-blind, parallel group study according to GCP procedure. **Study population**: Male and female outpatients aged 65 to 89 years, with mild to moderate essential hypertension. **Blinding**: The study was double blind. Blinding of the treatment was obtained using encapsulated drugs. Blinding treatment code was sealed and held by investigators, and could be broken only for safety reasons. An open label phase was foreseen after the double-blind period (see below). **Randomisation**: A randomisation list was prepared using blocks, and stratified by centre.
Number of patients (planned and analysed): Planned: 350 to be randomised (175 by treatment group), to have 300 evaluable patients. Screened: 419. Randomised: 351. Analysed: 345 (double-blind phase). Number of centres: Planned: 38. Each centre had to include 10 patients (5 patients per arm). Actual: 49 (31 enrolled patients)
Diagnosis and main criteria for inclusion: New diagnosis of grade 1 or 2 essential arterial hypertension (sitting clinic SBP 140-179 mmHg and/or sitting clinic DBP 90-109 mmHg) or essential arterial hypertension not controlled with current treatment or with intolerance to current treatment
Test products, dose and mode of administration: Capsules containing olmesartan 10, 20 or 40 mg tablets were used during the double-blind period, following 2 weeks of placebo run-in. All test products adhered to good manufacturing practices (GMP). The starting treatment dose of olmesartan was 10 mg. During the double-blind phase patients not normalised (BP ≥140/90 mmHg for non diabetic patients and BP ≥130/80 mmHg for diabetic patients) at each visit had to receive a double dose of the study drug, until a maximum dose of 40 mg/day.

Statistical methods:

A Chi-square test was used for between-treatment comparison of the primary variable. The odds ratio of normalised patients with 95% confidence interval (CI) was computed. The same test was applied to secondary categorical variables. For the continuous secondary variables an analysis of covariance (ANCOVA) was applied using baseline as covariate and treatment as main effect.

Analysis of the open label period was kept descriptive.

All statistical analyses were two-sided. All comparisons were tested at the 5% level of significance.

Concerning the safety analysis, the number of patients reporting AEs and the types of AE were summarised by treatment group. Vital signs were listed and summary statistics presented. Abnormal laboratory data were presented, along with ECG findings. Concomitant medications were summarised and listed. No formal statistical analyses were performed.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS: A total of 419 patients entered the screening phase of the study, 351 (83.8%) were randomised to active treatment, and 294 (83.8%) completed the double-blind phase. The most common reasons for dropping-out from the study were occurrence of an AE (n=14), withdrawal of consent (n=9) and protocol violation (n=7). 98 randomised patients entered and 80 completed the open label phase. Number of patients with valid ABP recordings at baseline and at the end of the double-blind phase was in total 85, those with valid ABPM at the end of the open label phase were 8.

The ITT population consisted of 345 patients (170 olmesartan and 175 ramipril), while the PP population was formed by 265 patients (137 olmesartan and 128 ramipril), for the double-blind period. The ITT population for the ABPM subgroup and for the double blind period was formed by 38 patients for the olmesartan group and by 47 patients for the ramipril group. PP population consisted of 32 patients randomised to olmesartan and by 42 patients randomised to ramipril. In the open phase the patients valid for ITT analysis were 95 and those for the PP analysis 77 (clinic BP). For the ABPM subgroup, the numbers for the ITT and PP population were 8 and 7, respectively.

Compliance to treatment was similar in the olmesartan and ramipril groups.

In the next paragraphs, results are summarised for the ITT population. No substantial difference was observed between the ITT and PP population for all efficacy variables.

Clinic BP during the double-blind phase

The full dose of olmesartan was taken at the end of the double-blind period by 66.0% of patients and the full dose of ramipril by 73.9% of patients. The average study drug dose at the end of the double-blind period was 31.9±11.7 mg for olmesartan (80% of the maximal dose) and 8.5±2.6 mg for ramipril (85% of the maximal dose). The rate of patients with sitting clinic DBP normalisation was larger in the olmesartan group (65.9% vs. 57.1% ramipril) even is not statistically significant. The same was true for the rate of DBP normalised plus DBP responder patients (68.8% vs. 62.9%).

Conversely, the rate of normalised patients at the end of the double-blind period was significantly ($p<0.05$) larger under olmesartan (38.8%) than ramipril (26.3%). This was the case also for the percentage of normalised plus responder patients (50.0% olmesartan vs. 37.7% ramipril, $p<0.05$). The proportion of normalised patients progressively increased during the double-blind treatment phase: the difference in favour of olmesartan for this variable was larger than that observed under ramipril also at week 2 (17.0% vs. 11.0%) and 6 (26.0% vs. 18.0%), with no statistically significant difference between the two groups.

Baseline-adjusted reductions in sitting clinic SBP, DBP and PBP were slightly, but not significantly larger under olmesartan (mean±SD: 16.6±17.5 mmHg SBP, 11.8±9.6 mmHg DBP and 4.8±13.7 mmHg PBP) than under ramipril (13.0±17.2 mmHg, 10.5±10.2 mmHg and 2.5±14.3 mmHg). Similarity in the BP lowering effect of olmesartan and ramipril was evident throughout the whole double-blind period. Antihypertensive effect of olmesartan and ramipril was similar also in the subgroup of 79 diabetic patients.

ABP during the double-blind phase

Baseline adjusted mean 24h SBP and DBP reductions were significantly greater ($p<0.01$) under olmesartan [mean and 95% CI: 8.9 (9.8 / 8.1) mmHg SBP and 5.7 (6.3 / 5.1) mmHg DBP] than under ramipril [6.7 (7.9 / 5.6) mmHg and 4.4 (5.1 / 3.7) mmHg]. Magnitude of the 24h PBP reduction did not significantly differ between treatment groups [3.3 (3.8 / 2.7) mmHg olmesartan and 2.4 (3.1 / 1.6) mmHg ramipril]. BP reductions under olmesartan were significantly ($p<0.01$) greater than under ramipril, also for the day-time, but not for the night-time sub period. Average hourly reductions were significantly larger with olmesartan than with ramipril in the last 4h from the drug intake [SBP: 11.0 (13.1 / 8.9) mmHg olmesartan vs. 3.7 (5.0 / 2.3) mmHg ramipril, $p<0.01$; DBP: 6.8 (9.3 / 4.3) mmHg vs. 3.2 (5.2 / 1.2) mmHg, $p<0.05$]. A good BP control was obtained by olmesartan also in the morning between 6 and noon. Rate of 24h BP normalisation (<135/80 mmHg) was significantly ($p<0.01$) larger under olmesartan (60.5% vs. 31.9% ramipril).

Open label phase

Most of the patients with sitting clinic DBP normalisation at the end of the double-blind period (63.2%) had their BP under control at the end of the open label period (80.0%). In the subgroup of diabetic patients, DBP normalisation rate increased from 40.9% to 69.1%.

During the open label phase clinic SBP and DBP were further significantly reduced by treatment (8.1±15.7 mmHg and 4.9±10.5 mmHg, $p<0.01$). This was observed for all visits, for all patients, and for the subgroups of patients taking monotherapy or with diabetes.

Analysis of ABPM data during the open label period could not be carried out because of the limited number of patients available.

Patients taking olmesartan 40 mg/day at the end of the 12-week double-blind treatment period could continue an open treatment with the drug for a further 36 weeks. During this open phase, non-diabetic patients not normalised at the end of the double-blind phase had to be treated with the addition of hydrochlorothiazide (HCTZ) 12.5 mg/day which could be doubled to 25 mg/day at the subsequent visit in case of lack of BP normalisation. Diabetic patients not normalised (SBP ≥130 mmHg and DBP ≥80 mmHg) after double-blind phase had to be treated with the addition of zofenopril 15 mg/day (7.5 mg/day in patients with a creatinine clearance <45 ml/min and/or with mild to moderate hepatic impairment), which could be doubled to 30 mg/day (or 15 mg/day) in case of non-normalisation. In case patients were not normalised with the highest drug dose combination (olmesartan 40 mg plus HCTZ 25 mg or olmesartan 40 mg plus zofenopril 30 mg or olmesartan 40 mg plus zofenopril 15 mg), they had to be withdrawn from the study.

The study medication was taken once a day between 8-10 a.m. all days except on the visit days when the patient was asked to take the medication after all the examinations had been completed. Patients were instructed to swallow the tablet and the capsule with a glass of water.

Duration of treatment:

84 days (12 weeks) double-blind. 252 days (36 weeks) open label.

Reference therapy, dose and mode of administration:

Capsules containing ramipril 2.5, 5 or 10 mg. The starting treatment dose was 2.5 mg. Ramipril up-titration followed the same scheme as for olmesartan (see above).

Criteria for evaluation:

Efficacy:

All efficacy variables were analysed on the intention-to-treat (ITT, all randomised patients who have taken at least one dose of the study drug and performed at least one measurement of the BP after the randomisation) and per-protocol population (PP, all randomised patients who have satisfied all inclusion criteria and no exclusion criteria and have completed the study respecting the specified protocol, with no major protocol violations).

The primary efficacy variable was the between-treatment comparison in the percentage of clinic sitting DBP normalised patients (<90 mmHg in non diabetic patients and <80 mmHg in diabetic patients) at the end of double-blind treatment (visit 3, 12 weeks of treatment).

The secondary efficacy variables were the between-treatment comparison in the:

- The percentage of normalised (sitting clinic SBP <140 mmHg and DBP <90 mmHg for non diabetic patients and sitting clinic SBP <130 mmHg and DBP <80 mmHg for diabetic patients) and responder patients (reduction of 20 mmHg in SBP and 10 mmHg in DBP) after 2, 6 and 12 weeks of treatment
- Changes in sitting clinic SBP and DBP at the end of the double-blind period (12 weeks)
- Changes in PBP (calculated as SBP minus DBP) at the end of the double-blind phase (12 weeks)
- Parameters of 24h ABPM:
  - Change from baseline to end of double-blind phase (visit 3) and open label period (visit 8) in the 24h mean SBP, DBP, HR and PBP
  - Change from baseline to end of double-blind phase (visit 3) and open label period (visit 8) in the day-time mean SBP, DBP, HR and PBP
  - Change from baseline to end of double-blind phase (visit 3) and open label period (visit 8) in the night-time mean SBP, DBP, HR and PBP
  - Proportion of ABPM responder patients, defined as patients with a decrease in mean SBP ≥15 mmHg and/or a decrease in mean DBP ≥10 mmHg, during the first 12h of the recording at the end of double-blind phase (visit 3) and open label period (visit 8)
  - Proportion of ABPM normalised patients defined as patients with a mean 24h SBP <125 mmHg and a mean 24h DBP <80 mmHg at the end of double-blind phase (visit 3) and open label period (visit 8)
  - Proportion of ABPM normalised patients defined as patients with a mean 24h SBP <135 mmHg and a mean 24h DBP <80 mmHg at the end of double-blind phase (visit 3) and open label period (visit 8)
  - Smoothness Index (SI) for the DBP and SBP at the end of double-blind phase (visit 3) and open label period (visit 8). The SI was computed as the ratio between the average of 24 hourly changes from baseline and the corresponding standard deviation. The higher this index, the greater is the homogeneity of the blood pressure control by antihypertensive treatment

Compliance: it was computed at each study visit as the ratio between the number of galenic units taken and the number of galenic units which should have been taken. The result was expressed as a percentage.

Safety:

All randomised patients taking at least one dose of active study drug were included in the safety analysis. The extent of exposure, the total number of adverse events (AE) reported, the number of AEs leading to discontinuation of the study drugs and the number of patients having developed at least one AE or serious adverse event (SAE) was collected.

SAFETY RESULTS:

During the placebo wash-out period 11 patients reported an AE, of which 5 were judged as drug related. All these patients were screening failures.

Double-blind phase

A total of 100 AEs were reported in 71 (20.2%) patients in the double-blind phase: approximately half of them (43.0%) were of mild intensity.

There were 19 drug related AEs (19.0% of all events), of which the majority (57.9%) were of a mild intensity. Overall 15 patients experienced drug-related AEs (21.1%). Thus the extent of drug adverse reactions was limited to at most one-fifth of the treated patients.

The number of AEs (41 olmesartan and 59 ramipril) and the proportion of patients who experienced AEs (18.5% vs. 21.9%) were similar between the two study groups. The greatest proportion of AEs was a respiratory, thoracic and mediastinal disorder (24%), musculoskeletal and connective tissue disorder (16%), nervous system disorder (12%) or gastrointestinal disorder (10%). Cough was much more commonly observed in the ramipril group. The number of AEs leading to study drug discontinuation was 18 (18.0% of all AEs) and occurred in 15 (21.1% of patients with AEs) patients (25.0% of patients with AE under olmesartan and 17.9% of patients with AE under ramipril).

5 SAEs were reported in 3 patients, but in no case was the SAE judged as related to study medication. In 1 patient the SAE led to study drug discontinuation. No death occurred during this phase of the study.

Open label phase

A total of 59 AEs were recorded in 42 patients (42.9%) in the open label phase: a small number of them were drug related (13.6%), while the majority were of mild intensity. The proportion of patients with AEs during the open label phase was larger than that of the double-blind phase (42.9%).

The number of AEs leading to study drug discontinuation was 7 (11.9% of all AEs) and occurred in 4 patients (9.5%).

4 SAEs were reported by 4 patients: none of them were drug related and one (myocardial infarction) caused the death of the patient.

Few patients displayed significant changes in laboratory values during the study, and there were no remarkable or consistent trends in abnormal haematological or biochemical findings between of the treatment groups.

No overt change occurred in urinary parameters (namely glucose, protein or blood in urine) at end of study versus baseline.

A slight reduction in clinic and ambulatory HR was observed with both treatments, with no remarkable between-treatment difference. No differences were observed for physical examination performed at baseline and along the study for each patient.

There was no difference with regards to the incidence of abnormalities in ECG between treatment groups. No consistent trends in the number of changes from normal to abnormal ECG findings between baseline and end of treatment were observed.

CONCLUSION:

The results of the present study demonstrated the greater efficacy of olmesartan 10 to 40 mg as compared to ramipril 2.5 to 10 mg in normalising both clinic SBP and DBP, though the primary efficacy variable (proportion of patients with sitting clinic DBP normalisation) was not significantly different between the two treatment groups. No differences were observed also for the subgroup of diabetic patients.

SBP and DBP reductions over the 24h by ABPM were significantly greater under olmesartan than under ramipril, as well as the reductions in the last 4h from drug intake and in the early morning (6-12 a.m.), suggesting a consistent and long-lasting and homogeneous BP control throughout the dosing interval.

Clinic BPs were further reduced during the open label period, in the group taking olmesartan monotherapy with eventual addition of HCTZ or zofenopril as required.

Both olmesartan medoxomil and ramipril were well tolerated, but the former was associated with a lower rate of cough, which was indeed the most common complaint among the treatment-emergent AEs recorded in the ramipril group.

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