Drugs 2007; 67 (1): 95-106
0012-6667/07/0001-0095/$49.95/0

Fixed-Dose Combination Lercanidipine/Enalapril

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Contents

Abstract

▲ Lercanidipine, a dihydropyridine calcium channel blocker, and enalapril, an ACE inhibitor, are established antihypertensive agents. A fixed-dose tablet formulation of lercanidipine/enalapril is approved in Germany for the treatment of hypertension in patients not responding to monotherapy.

▲ Lercanidipine/enalapril 10mg/10mg once daily significantly reduced sitting diastolic blood pressure and sitting systolic blood pressure, relative to lercanidipine 10mg once daily, in a 12-week, randomised, double-blind trial in patients with mild to moderate hypertension who had previously not responded to 4 weeks' treatment with lercanidipine.

▲ In a similarly designed trial, lercanidipine/enalapril 10mg/20mg once daily was significantly more effective than enalapril 20mg once daily in hypertensive patients who had previously not responded to enalapril monotherapy.

▲ Fixed-dose lercanidipine/enalapril was generally well tolerated, with a tolerability profile similar to that of either of the individual drugs alone or placebo. Cough was reported in ≤5.2% and peripheral oedema in ≤1.5% of lercanidipine/enalapril recipients.

Features and properties of fixed-dose combination lercanidipine/enalapril (Zanipress®, Zanitek®)	
Indication	
Hypertension not adequately controlled by monotherapy with lercanidipine or enalapril	
Mechanism of action	
Lercanidipine inhibits calcium entry through L-type channels into vascular smooth muscle cells; enalaprilat, the active metabolite of enalapril, inhibits angiotensin converting enzyme, thereby reducing levels of angiotensin II	
Dosage and administration	
Recommended dose	Lercanidipine/enalapril 10mg/10mg in nonresponders to lercanidipine; lercanidipine/enalapril 10mg/20mg in nonresponders to enalapril
Route of administration	Oral
Frequency of administration	Once daily, ≥15 min before a meal
Steady-state pharmacokinetics of *S*-lercanidipine (S-LER), enalapril (EN) and enalaprilat (ENL) in patients (n = 20) with essential hypertension (lercanidipine/enalapril 10mg/20mg capsule once daily for 8 days)	
Peak plasma concentration (S-LER; EN; ENL)	3.6; 91; 53 μg/L
Time to peak plasma concentration (S-LER; EN; ENL)	1; 1; 4 hours
Adverse events	
Most frequent	Cough, headache, dizziness, peripheral oedema, flushing, vertigo

Hypertension is a significant factor in the development of cerebrovascular disorders, heart disease and renal failure, and is estimated to contribute to ≈5% of the global disease burden.[1] The consequences of hypertension represent a continuum of a progressive cardiovascular syndrome, rather than just elevated blood pressure (BP) alone, leading to structural and functional changes in the heart and vascular system.[2] The aim of treatment is to reduce the long-term risk of cardiovascular morbidity and mortality, by targeting not only raised BP but also risk factors such as diabetes mellitus.[3]

Reduction of systolic BP (SBP) to the desired target value (<140mm Hg, or <130mm Hg in patients with diabetes mellitus or renal disease) is not easily achieved with a single antihypertensive medication; a combination of drugs is required in a large proportion of patients to achieve this goal.[3-5] A combination regimen is more likely to achieve BP control if the component drugs have different mechanisms of action, since elevated BP is the result of a multifactorial process.[3-5]

Combining a calcium channel blocker (CCB) with an ACE inhibitor is one of the combination regimens recommended in several antihypertensive guidelines;[3-5] one such potential regimen is fixed-dose lercanidipine/enalapril. Lercanidipine, a dihydropyridine CCB, induces vascular relaxation, with a consequent decline in vascular resistance and arterial pressure.[5] However, this class of drugs is also likely to have some undesirable effects (e.g. peripheral oedema), as a result of activation of both the sympathetic nervous system and the renin-angiotensin-aldosterone axis.[6] The concomitant administration of an ACE inhibitor, such as enalapril, may counteract these unwanted effects.[6] A further advantage of ACE inhibitors is their potential to reduce the incidence of new-onset diabetes.[7] Furthermore, administering the agents as an individual fixed-dose tablet or gelatin capsule is likely to provide several potential advantages over separate administration, such as lower dose, improved patient compliance and greater cost effectiveness.[6]

Lercanidipine[8,9] and enalapril[10,11] are well established therapies for hypertension, and have been reviewed previously in *Drugs*. This review focuses on the use of oral fixed-dose lercanidipine/enalapril (Zanipress®, Zanitek®)[1] in the treatment of adult patients with essential hypertension.

1. Pharmacodynamic Profile

No published pharmacodynamic data are available for the combination of lercanidipine and enalapril; consequently, a brief overview of the pharmacodynamics of the individual drugs, based largely on previous reviews,[8-11] is provided in this section.

Lercanidipine

- Lercanidipine inhibits calcium entry through L-type calcium channels, for which the *S*-enantiomer has 100- to 200-fold higher affinity than the *R*-enantiomer, in smooth muscle cells of the cardiovascular system, resulting in peripheral vasodilation and reduced BP.[8,9,12] Antihypertensive effects have a gradual onset and long duration, relative to those of other CCBs such as nifedipine and nitrendipine.[8,9]
- *In vitro* data indicate that lercanidipine is highly selective for vascular smooth muscle, relative to cardiac tissue,[8,9] possibly as a result of a greater proportion of L-type Ca^{2+} channels existing in a high-affinity inactivated state that is readily blocked by lercanidipine.[13]
- Lercanidipine may have antiatherogenic effects that are independent of its BP-lowering effects.[8,9,14-17] In hypertensive patients with coexisting type 2 diabetes, lercanidipine 10 mg/day for 16 weeks reduced levels of low-density lipoprotein-cholesterol oxidation (measured as conjugated diene formation) by 35% relative to baseline ($p < 0.001$).[16] The drug also delayed the development of fatty streaks and hyperplastic lesions in a rabbit model,[14] and inhibited smooth muscle cell proliferation and migration[15] and the release of

1 The use of trade names is for product identification purposes only and does not imply endorsement.

metalloproteinases and esterification of cholesterol in macrophages[17] *in vitro*.

- Lercanidipine appears to have no clinically relevant effects on heart rate or ECG parameters in patients with hypertension.[9] In addition, there was no significant change from baseline in left ventricular mass in 23 patients with hypertension who received 6 months' treatment with lercanidipine (10mg once daily for the first 4 weeks and then 10 or 20mg once daily).[18]
- Lercanidipine 10[19,20] or 20[20] mg/day also appears to have renoprotective effects; creatinine clearance (CL_{CR}) was increased by 10% ($p = 0.019$) in hypertensive patients with renal dysfunction (CL_{CR} <80 mL/min [<4.8 L/h]) over 6 months,[19] and albumin excretion was reduced by 20% ($p < 0.05$) in hypertensive patients with microalbuminuria and type 2 diabetes over 12 months.[20] In spontaneously hypertensive rats, lercanidipine inhibited glomerular hypertrophy (18%),[21] vasodilated afferent (23% reduction in wall-to-lumen ratio) and efferent (19% reduction in wall-to-lumen ratio) glomerular arterioles[22] and reduced albuminuria (28%)[22] [all $p < 0.05$ vs baseline].
- Lercanidipine 10–30mg once daily for 24–48 weeks had neutral or favourable effects on lipids in patients with hypertension, while doses of 10 or 20 mg/day improved glucose tolerance and reduced fasting blood glucose, glycosylated haemoglobin and serum fructosamine levels in hypertensive patients with type 2 diabetes after 8 weeks.[9]

Enalapril

- Enalapril is an orally administered prodrug that is hydrolysed to form the active ACE inhibitor enalaprilat (see section 2), reducing plasma levels of the potent vasoconstrictor angiotensin II, with a consequent decrease in aldosterone secretion and an increase in plasma renin activity.[11] The reduction in angiotensin II levels results in peripheral vasodilation and reduced vascular resistance, leading to decreased BP.[10,11,23] Enalapril has little effect on heart rate or cardiac output.[11]
- Enalapril dose-dependently reduces BP in hypertensive patients at doses ≤10mg, with the maximum effect occurring 6–8 hours after administration; higher doses prolong the duration of the BP-lowering effect to a total of 24–36 hours.[10]
- Enalapril 10 or 20 mg/day (n = 7) for 12 months decreased both the media-to-lumen ratio (from 0.117 to 0.093; $p < 0.01$) in subcutaneous small arteries and left ventricular mass index (from 94.8 to 78.7 g/m^2; $p < 0.05$) in patients with hypertension and type 2 diabetes (n = 15).[24] Small artery remodelling is regarded as an early indicator of end-organ damage as it not only increases peripheral resistance but also impedes blood supply to organs such as heart, brain and kidney, thereby contributing to complications of hypertension.[25]
- Enalapril 10 or 20 mg/day changed carotid artery intima-media thickness (IMT) by −0.080mm (95% CI −0.097, −0.063) in hypertensive patients after 2 years' treatment (abstract presentation),[26] and enalapril 10 mg/day (n = 48) halved the annual increase in IMT in patients with type 2 diabetes relative to a control group (n = 50) that did not receive enalapril (0.01 vs 0.02mm; $p < 0.05$).[27] Increased IMT is associated with increased risk of cardiovascular and cerebrovascular disease.[27]
- Enalapril improves some atherosclerotic risk factors; an index of platelet activation (the ratio of β-thromboglobulin to platelet factor 4) was significantly decreased ($p < 0.05$ vs baseline) at a dosage of 20 mg/day for ≥4 weeks in 12 patients with essential hypertension,[28] and plasma levels of intercellular adhesion molecule-1 were significantly reduced ($p < 0.01$ vs baseline) at a dosage of 10,[29] 20 or 40[30] mg/day for 24 weeks in 57 patients with essential hypertension and type 2 diabetes[29] and 21 patients with hypertension (abstract presentation).[30]
- Potentiation of the effects of bradykinin may contribute to the apparent cardiovascular protection associated with enalapril treatment.[31] In patients with atypical chest pain, enalapril 10mg once daily for 7 days (n = 25) significantly ($p < 0.0001$) increased bradykinin-induced release of tissue plasminogen activator in the coronary circulation relative to that in a control group (n = 31) that did not receive enalapril.[31] Enalapril may inhibit degradation of

bradykinin, as angiotensin converting enzyme also functions as kininase II.[23]

- ACE inhibitors have been reported to have renoprotective effects by reducing glomerular capillary pressure.[32] In a randomised, double-blind, 6-year trial in patients with type 2 diabetes and normoalbuminuria at baseline, 5 of 77 (6.5%) enalapril 5–10 mg/day recipients and 15 of 79 (19.0%) placebo recipients developed microalbuminuria (urinary albumin excretion >30 mg/24h) [p = 0.001]; long-acting CCBs (diltiazem or verapamil) and/or hydrochlorothiazide were used for BP control when SBP/diastolic BP (DBP) was consistently ≥145/95mm Hg.[33]
- However, enalapril 10mg once daily did not affect the long-term development of nephropathy in 18 patients with type 1 diabetes and albuminuria.[34] After 6 months, enalapril significantly ($p < 0.05$) reduced the median albumin excretion rate (from 148 to 90 μg/min), but this decrease was not maintained at 3 years.[34]

2. Pharmacokinetic Profile

The pharmacokinetic profile of a fixed-dose gelatin capsule of lercanidipine/enalapril 10mg/20mg (used in a phase III trial;[35] see section 3) was similar to that of the individual agents, based on absorption parameters, in a multiple-dose, randomised, double-blind, crossover study in 20 patients with essential hypertension (DBP ≥95mm Hg).[36] At steady state (on day 8), peak plasma concentration (C_{max}) values of *S*-lercanidipine, enalapril and enalaprilat were 3.6, 91 and 53 μg/L, respectively, at 1, 1 and 4 hours after administration of the combination.[36] In addition, the fixed-dose gelatin capsule was bioequivalent to a fixed-dose tablet formulation of lercanidipine/enalapril 10mg/20mg (intended for marketing) in a single-dose, randomised, open-label, crossover study in 48 healthy volunteers; the confidence intervals for the tablet **:** capsule ratios of the area under the plasma concentration-time curve (AUC) and C_{max} for lercanidipine enantiomers, enalapril and enalaprilat were within the bioequivalence acceptance range of 0.80–1.25.[37] Thus, discussion in this section focuses on the well established pharmacokinetic profiles of the individual agents, lercanidipine[8,9] and enalapril,[10,11] including data from the prescribing information.[12,23]

Lercanidipine

Since the pharmacological activity of racemic lercanidipine is mainly attributed to the *S*-enantiomer (section 1), and no *in vivo* interconversion of the *S*- and *R*-enantiomers has been demonstrated,[12] discussion in this section focuses on the pharmacokinetic profile of *S*-lercanidipine.

- After oral administration of racemic lercanidipine, *S*-lercanidipine is completely absorbed from the gastrointestinal tract and exhibits nonlinear pharmacokinetics.[9] Lercanidipine should be administered prior to meals, as the absorption of *S*-lercanidipine is increased 4-fold when it is administered after a high-fat meal.[8,12]
- Lercanidipine exhibits a high level of plasma protein binding (>98%) and is lipophilic, aggregating in lipid membranes of arterial wall cells.[8,9,12] The magnitude of the apparent volume of distribution (2–2.5 L/kg for intravenous infusion of lercanidipine 2mg) has been ascribed to the high lipophilicity of the drug.[9] In addition, the absolute bioavailability of lercanidipine in fed hypertensive patients is about 10%.[12]
- Lercanidipine is metabolised by cytochrome P450 (CYP) 3A4, and undergoes substantial first-pass metabolism; the resulting metabolites are mainly inactive.[9] The drug is excreted as metabolites in both urine and faeces (43.8% and 50.4% after administration of lercanidipine 20mg in healthy volunteers).[38] After oral administration of lercanidipine 10mg in patients with mild to moderate hypertension, the mean plasma terminal elimination half-life ($t_{1/2}\beta$) was 8.0 hours.[9]
- Coadministration of lercanidipine and strong inhibitors of CYP3A4 is not advised,[12] and caution is recommended when coadministering lercanidipine and inducers or other substrates of CYP3A4. [12] The drug should not be coadministered with ciclosporin or grapefruit juice.[12] Lercanidipine may increase C_{max} of digoxin; patients receiving both drugs

should be monitored for digoxin toxicity.[12] Lercanidipine does not interact significantly with warfarin, simvastatin, diuretics or ACE inhibitors.[12]

- The use of lercanidipine in patients with severe hepatic or renal impairment is not recommended because of the risk of drug accumulation.[8,9,12] Caution is advised when increasing the dose of lercanidipine to 20mg once daily in patients with mild to moderate hepatic or renal impairment.[12]

Enalapril

- Enalapril is de-esterified in the liver to form enalaprilat, which does not undergo further metabolism.[10,11] The C_{max} of enalaprilat is linearly related to the dose of enalapril across the 2.5–40mg dose range;[10,11] however, the AUC for enalaprilat is not linearly related to enalapril dosage because of the prolonged terminal elimination phase.[10,11]
- The absolute bioavailability of oral enalapril as enalaprilat is approximately 40%,[11] and no more than 60% of circulating enalaprilat is bound to human plasma proteins.[23] Enalapril crosses the placental barrier; consequently, the drug is contraindicated in pregnant patients.[11,23]
- Enalaprilat is eliminated predominantly by the renal route.[10] There is an initial elimination phase followed by a prolonged terminal phase, with respective $t_{1/2}$ values of ≈5 hours and 30–35 hours.[11] The latter phase represents tight binding to plasma angiotensin converting enzyme.[11] Following multiple doses of enalapril, the effective $t_{1/2}$ of enalaprilat is 11 hours.[23]
- Dose reduction of enalapril is necessary in patients with renal impairment (CL_{CR} <80 mL/min), to reduce the risk of drug accumulation.[23] However, dosage adjustment is not necessary in patients with hepatic dysfunction.[11]
- A retrospective analysis of 20 hypertensive patients demonstrated the possibility of an increase in serum lithium concentrations when it was coadministered with ACE inhibitors, including enalapril.[39] This was particularly evident in patients ≥50 years old (n = 12).[39] However, in a study in healthy volunteers (n = 9), enalapril did not significantly affect serum lithium concentrations.[40] Nevertheless, concomitant use of enalapril and lithium is not recommended; if coadministration of these agents is unavoidable, then serum lithium concentrations should be closely monitored.[23]

3. Therapeutic Efficacy

The efficacy of oral, once-daily, fixed-dose lercanidipine/enalapril gelatin capsules has been evaluated in adult patients with mild to moderate essential hypertension in a randomised, double-blind, multicentre, phase II, dose-finding trial (study CPL2-0008)[41] and two 12-week, multicentre, phase III trials (studies CPL1-0018[42] and CPL1-0019[35]), with longer-term efficacy evaluated in noncomparative 9-month extensions of the phase III trials.[35,42] Data are currently available only as data on file.[35,41,42]

These data are supported by results from a randomised, double-blind trial, in which patients with mild to moderate hypertension who had not responded to 4 weeks of treatment with enalapril 20 mg/day received lercanidipine 10 mg/day (n = 56) or hydrochlorothiazide 12.5 mg/day (n = 56) as add-on therapy to enalapril for 20 weeks; lercanidipine was non-inferior to hydrochlorothiazide for reduction of sitting DBP (sDBP) at trough levels (primary endpoint; reduction of 9.3 vs 7.4mm Hg [baseline 97mm Hg]).[43]

All trials of fixed-dose lercanidipine/enalapril had an initial washout period of 11–17 days[41] or ≥5 half-lives of any previously administered antihypertensive agents,[35,42] followed by a single-blind placebo run-in phase of 2 weeks[35,42] or 25–31 days.[41]

Mild to moderate hypertension was defined in the phase II trial as sDBP values in the range 95–109mm Hg both before and after the washout phase and also during and after the placebo run-in phase,[41] and in phase III trials as sitting SBP (sSBP) in the range 140–189mm Hg and sDBP in the range 95–114mm Hg both before and after the placebo run-in period.[35,42] Exclusion criteria included secondary hypertension, cardiovascular disease (with the exception of stable angina pectoris, uncomplicated hypertensive cardiovascular disease, or uncomplicated myocardial infarction at least 6

months previously), cardiovascular surgery within the previous 6 months, a history of hypertensive encephalopathy or cerebrovascular accident, uncontrolled or complicated diabetes, hypertensive retinopathy or use of any medications (except NSAIDs) that could affect BP.[35,41,42]

There were no between-group differences in the randomised trials in terms of patient characteristics at baseline (the start of the double-blind phase),[35,41,42] with the exception of one trial (CPL1-0018)[42] where the mean age in the fixed-dose combination group was 53.5 versus 51.0 years in the monotherapy group ($p = 0.026$).

Analyses were based on the intent-to-treat (ITT) population, which was defined as all patients who had received at least one dose of treatment in the double-blind phase and had ≥1 BP measurement 18–48 hours after this point, with the last observation carried forward in the event of premature withdrawal.[35,41,42] Statistical analyses were based on an analysis of covariance, with treatment and centre as main effects and baseline value as a covariate.[35,41,42]

Phase II Dose-Finding Trial

The appropriate once-daily fixed-dose combination was determined using various combinations of lercanidipine (5, 10 or 20mg), enalapril (5 or 10mg) and placebo, in an ITT population of 653 patients (n = 51–63/group).[41] The primary endpoint was the change in trough sDBP (measured 22–26 hours post-dose) from baseline after 8 weeks of double-blind treatment, assessed using a dose-response surface analysis (as recommended by the European Agency for the Evaluation of Medicinal Products[44]).[41]

- Based on the additive response surface model analysis of the primary endpoint, once-daily lercanidipine/enalapril 10mg/10mg was the optimal fixed-dose combination.[41] The estimated change in trough sDBP after 8 weeks was significantly greater in recipients of lercanidipine/enalapril 10mg/10mg once daily (−10.4mm Hg; 95% CI −11.4, −9.5) than in lercanidipine 10mg once daily recipients (−8.2mm Hg; 95% CI −9.2, −7.3). Moreover, recipients of this fixed-dose combination achieved a similar reduction from baseline in sDBP to that observed in recipients of lercanidipine 20mg once daily (−9.9mm Hg; 95% CI −8.6, −11.2). Mean baseline sDBP was 100mm Hg in all groups.[41]
- Analysis of covariance indicated that monotherapy with once-daily lercanidipine 10 or 20mg or enalapril 10mg provided better antihypertensive efficacy than placebo (all $p < 0.05$); there were no between-group differences for 5mg doses of lercanidipine or enalapril versus placebo.[41] Notably, all fixed-dose combinations were superior to placebo in terms of antihypertensive efficacy (all $p < 0.05$).[41]
- Patient compliance (assessed by capsule count) was ≥98.5% in all treatment groups.[41]

Phase III Trials

The two phase III trials evaluated lercanidipine/enalapril fixed-dose combination therapy in hypertensive patients who were not responding to lercanidipine (study CPL1-0018)[42] or enalapril (study CPL1-0019)[35] monotherapy. During the single-blind monotherapy phase, patients received either lercanidipine 10mg once daily for 4 weeks (CPL1-0018)[42] or once-daily enalapril 10mg for 2 weeks, with the dosage increased to 20mg once daily for the next 4 weeks (CPL1-0019).[35] Nonresponders were defined as patients who had a trough sDBP of 95–109mm Hg after the single-blind monotherapy phase, while maintaining a trough sSBP of <180mm Hg.[35,42]

Nonresponders to lercanidipine monotherapy received once-daily lercanidipine/enalapril 10mg/10mg (n = 165) or once-daily lercanidipine 10mg monotherapy (n = 172) for 12 weeks.[42] Mean baseline sSBP/sDBP was 152/100mm Hg in both groups.[42] Nonresponders to enalapril monotherapy received once-daily lercanidipine/enalapril 10mg/20mg (n = 162) or once-daily enalapril 20mg monotherapy (n = 163) for 12 weeks; mean baseline sSBP/sDBP was 154/99mm Hg in both groups.[35]

In both trials, the primary efficacy endpoint was the change from baseline in mean trough sDBP after 12 weeks of double-blind treatment.[35,42] Secondary

endpoints included the change from baseline in mean trough sSBP after 12 weeks, the proportion of patients with normalised SBP (sSBP <140mm Hg), normalised DBP (sDBP <90mm Hg) or normalised SBP/DBP (sSBP/sDBP <140/90mm Hg) after 12 weeks, and the proportion of patients classed as responders after 12 weeks (normalised SBP or sSBP decreased from baseline by ≥20mm Hg; normalised DBP or sDBP decreased from baseline by ≥10mm Hg).[35,42]

- Lercanidipine/enalapril 10mg/10mg once daily showed better antihypertensive efficacy than lercanidipine 10mg once daily after 12 weeks in lercanidipine nonresponders, according to the primary endpoint (mean change in sDBP from baseline −7.1 vs −4.3mm Hg; $p < 0.001$).[42] The mean change in sSBP from baseline was also significantly ($p < 0.001$) greater in the combination therapy group (−7.7 vs −2.3mm Hg). Significantly (all $p < 0.001$) greater reductions in sDBP and sSBP in the fixed-dose combination group than in the monotherapy group occurred after 2 weeks and were maintained throughout the 12 weeks of the study.[42]

- In lercanidipine nonresponders, after 12 weeks' treatment, a significantly greater proportion of patients receiving the fixed-dose combination had normalised SBP (39% vs 22%; $p < 0.001$), normalised DBP (29% vs 19%; $p = 0.023$) and/or normalised SBP/DBP (22% vs 12%; $p = 0.012$) than lercanidipine monotherapy recipients.[42] The responder rate was also higher in combination therapy recipients than in lercanidipine monotherapy recipients (sSBP 41% vs 24%, $p < 0.001$; sDBP 35% vs 24%, $p = 0.032$).[42]

- Similarly, in enalapril nonresponders, the fixed-dose combination was more effective than enalapril monotherapy. After 12 weeks, the mean changes in trough sDBP from baseline were −9.2 and −7.5mm Hg in recipients of lercanidipine/enalapril 10mg/20mg once daily and enalapril 20mg once daily ($p = 0.015$).[35] The corresponding mean changes in sSBP from baseline were −9.8 and −6.7mm Hg ($p = 0.013$). Significant (all $p < 0.05$) between-group differences in favour of fixed-dose combination therapy were evident from 8 weeks onwards for sDBP and from 4 weeks onwards for sSBP. There was a numerically higher percentage of combination therapy, versus monotherapy, recipients with normalised DBP (48% vs 37%), normalised SBP (33% vs 28%), normalised SBP/DBP (24% vs 17%) or responder rate (sDBP 53% vs 43%, sSBP 41% vs 33%), but these differences did not attain statistical significance.[35]

- A subgroup analysis of elderly nonresponders to enalapril showed that the mean change from baseline in trough sDBP at 12 weeks was significantly (both $p < 0.05$) greater in combination therapy, versus monotherapy, among recipients aged >60 years (n = 164; −10.9 vs −7.9mm Hg) or ≥65 years (n = 101; combination therapy vs monotherapy treatment difference of −2.6mm Hg).[35] In these subgroups, the treatment differences for the change from baseline in trough sSBP did not reach statistical significance (combination therapy vs monotherapy treatment difference of −3.2 and −2mm Hg in patients aged >60 and ≥65 years).[35]

Extension Phase

Patients were eligible for inclusion in the noncomparative extension phase of each of the phase III trials if they had completed the double-blind treatment phase with an sSBP in the range of 120–179mm Hg and an sDBP in the range of 80–109mm Hg.[35,42] This phase was primarily designed to evaluate long-term tolerability (see section 4).

In the extension phase in nonresponders to lercanidipine monotherapy, 221 patients (110 fixed-dose combination and 111 lercanidipine recipients) received lercanidipine/enalapril 10mg/10mg once daily, with a switch to lercanidipine/enalapril 10mg/20mg once daily permitted if sSBP/sDBP was >140/90mm Hg; 201 patients completed 9 months' treatment in the extension phase.[42] In the extension phase in nonresponders to enalapril monotherapy, 186 patients (94 fixed-dose combination and 92 enalapril recipients) received lercanidipine/enalapril 10mg/20mg once daily; 164 patients completed 9 months' treatment.[35]

• Among lercanidipine monotherapy nonresponders, 52% of extension-phase combination therapy recipients achieved a normalised SBP, 46% a normalised DBP and 37% a normalised SBP/DBP after 9 months.[42] Among patients switched from lercanidipine/enalapril 10mg/10mg to lercanidipine/enalapril 10mg/20mg during the extension phase (n = 133; 60%), 35% achieved a normalised SBP, 33% a normalised DBP and 20% a normalised SBP/DBP.[42]

• Similarly, among nonresponders to enalapril monotherapy, 40% achieved a normalised SBP, 60% a normalised DBP and 36% a normalised SBP/DBP in the extension phase.[35]

4. Tolerability

The fixed-dose formulation of lercanidipine/enalapril was generally well tolerated for ≤52 weeks by patients with mild to moderate hypertension in the phase II and III trials[35,41,42] discussed in section 3. This section focuses on a pooled safety analysis[45] of all patients who received at least one dose of lercanidipine/enalapril 10mg/10mg or 10mg/20mg in these trials[35,41,42] or in a pharmacokinetic interaction trial[36] discussed in section 2.

• In the 8-week dose-finding trial (section 3), treatment-emergent adverse events occurred with similar frequencies in the fixed-dose combination groups to those observed in the lercanidipine and enalapril monotherapy or placebo groups.[41] The proportion of patients experiencing any treatment-emergent adverse event was 25.0–42.2% in the treatment groups and 36% in the placebo group. The most frequent treatment-related adverse events were headache (1.7–7.4%), coughing (1.7–9.8% in enalapril recipients and 0–1.9% in those not receiving enalapril) and dizziness (frequency not reported).[41] One lercanidipine/enalapril 20mg/10mg recipient experienced a serious adverse event (circulatory collapse) that was considered to be probably treatment-related.[41]

• Treatment-emergent adverse events considered to be at least possibly related to therapy occurred in 39 of 329 (11.9%) patients receiving lercanidipine/enalapril 10mg/10mg per day and 69 of 410 (16.8%) patients receiving lercanidipine/enalapril 10mg/20mg per day in the pooled analysis.[45] Common treatment-emergent adverse events are summarised in figure 1.[45]

• Discontinuation of treatment because of an adverse event occurred with a similar frequency in the combination therapy and monotherapy groups, with the incidence in lercanidipine/enalapril 10mg/10mg and 10mg/20mg groups being 4.6% and 4.4%; cough was the most common cause of treatment discontinuation (0.9% and 2.2%).[45]

• Cough and dizziness were two of the most common treatment-emergent adverse events that occurred with both lercanidipine/enalapril dosages (figure 1).[45] Cough was attributed to the enalapril

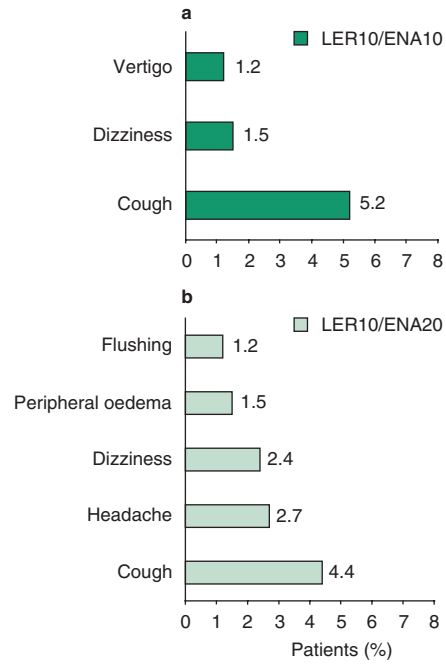

Fig. 1. Tolerability profile of once-daily, orally administered, fixed-dose lercanidipine/enalapril in patients with mild to moderate essential hypertension receiving (**a**) lercanidipine/enalapril 10mg/10mg per day (LER10/ENA10; n = 329) or (**b**) lercanidipine/enalapril 10mg/20mg per day (LER10/ENA20; n = 410) for ≤52 weeks. Treatment-emergent adverse events considered to be at least possibly related to therapy occurring in ≥1% of patients, using pooled data[45] from an 8-day, double-blind, pharmacokinetic interaction study,[36] an 8-week, double-blind, dose-finding study[41] and two 12-week, double-blind, phase III trials with 9-month, noncomparative extension phases.[35,42]

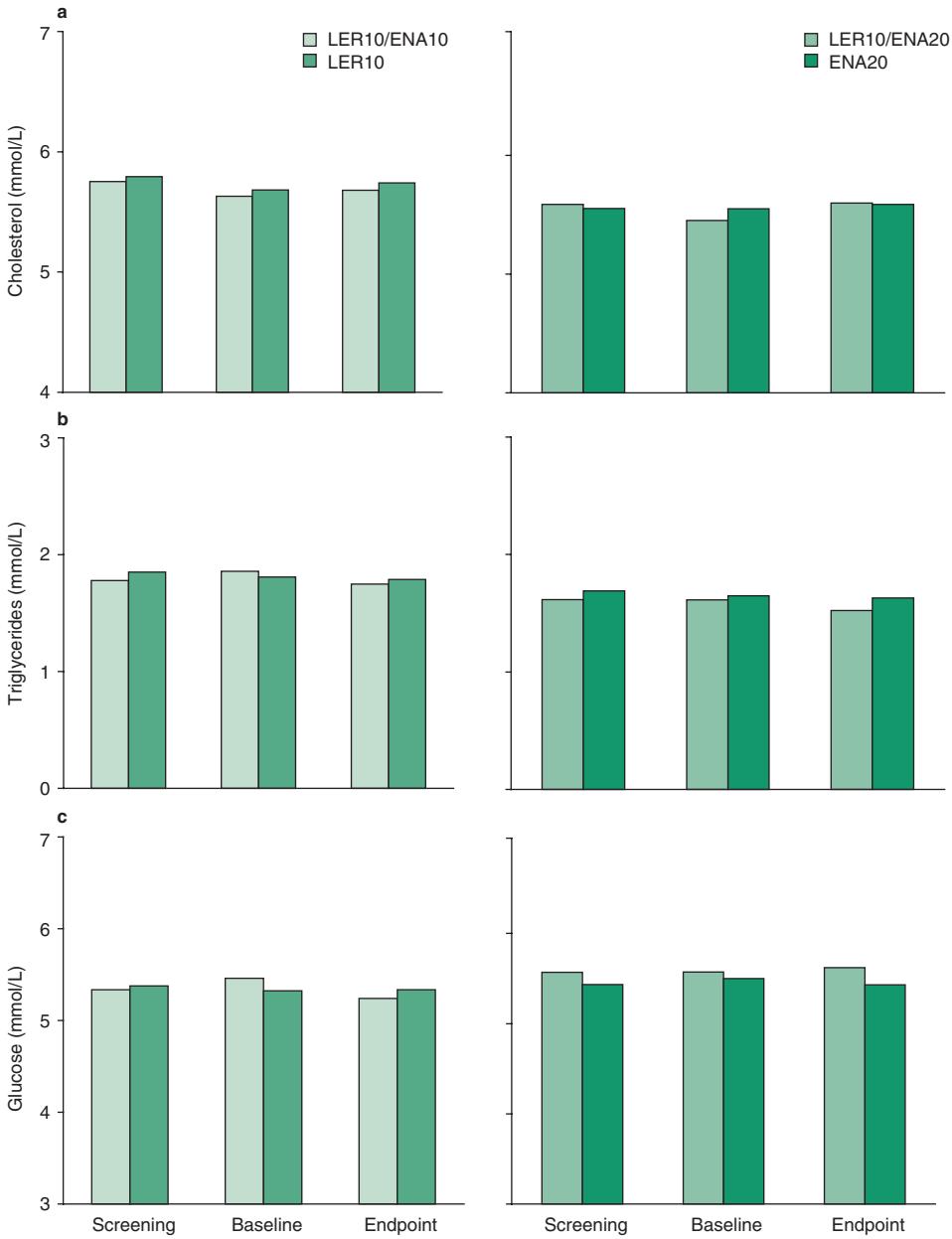

Fig. 2. Effect on plasma lipids and glucose of once-daily, orally administered, fixed-dose lercanidipine/enalapril or component drug in patients with mild to moderate essential hypertension. Mean values for (**a**) cholesterol, (**b**) triglycerides and (**c**) glucose in recipients of lercanidipine/enalapril 10mg/10mg per day (LER10/ENA10) [n = 167], lercanidipine 10 mg/day (LER10) [n = 175], lercanidipine/enalapril 10mg/20mg per day (LER10/ENA20) [n = 163] or enalapril 20 mg/day (ENA20) [n = 164] at screening, baseline and endpoint (the last measurement obtained during the 12-week double-blind treatment period). The normal ranges (fasting conditions) were <5.698 mmol/L (cholesterol), 0.56–2.15 mmol/L (triglycerides) and 3.33–5.55 mmol/L (glucose).[48] Data were derived from two randomised, double-blind trials: CPL1-0018,[46] in which patients received LER10/ENA10 or LER10, and CPL1-0019,[47] in which patients received LER10/ENA20 or ENA20.

component, whereas peripheral oedema and flushing were most likely due to lercanidipine-induced peripheral vasodilation. Dizziness and vertigo were considered to be possibly linked to the BP-lowering effect of the combination.[45]

- Serious adverse events occurred in 1.5% of lercanidipine/enalapril 10mg/10mg per day and 3.2% of lercanidipine/enalapril 10mg/20mg per day recipients in the pooled analysis, but all were considered to be either unrelated to treatment or unlikely to be related to treatment.[45]
- In the phase III trials (section 3), the proportion of patients with clinically significant abnormalities in plasma levels of lipids or glucose was low (≤8%) at both baseline and endpoint (the last measurement obtained during the 12-week treatment period) with lercanidipine/enalapril 10mg/10mg per day[42] or 10mg/20mg per day.[35] The mean values for plasma lipids and glucose at screening, baseline and endpoint in the phase III trials are shown in figure 2.[46,47]

5. Dosage and Administration

Fixed-dose combination lercanidipine/enalapril is indicated for the treatment of hypertension in patients aged ≥18 years;[49,50] the 10mg/10mg combination is used in patients in whom adequate BP control has not been achieved with lercanidipine monotherapy[49] and the 10mg/20mg combination is used in patients not achieving BP control with enalapril monotherapy.[50] The fixed-dose combination tablet is taken once daily at least 15 minutes before a meal.[49,50]

Lercanidipine/enalapril 10mg/10mg or 10mg/20mg tablets should not be administered during pregnancy or lactation.[49,50] Local prescribing information should be consulted for detailed information, including contraindications, precautions, drug interactions and use in special patient populations.

6. Lercanidipine/Enalapril: Current Status

In well controlled trials, once-daily administration of fixed-dose lercanidipine/enalapril has been shown to effectively lower BP in hypertensive patients inadequately controlled by either component drug, and was generally well tolerated. Only a small number of patients discontinued treatment because of an adverse event; simplification of the dosage regimen to a single once-daily capsule resulted in excellent compliance in the large phase II trial.

The absence of negative effects of the combination on lipid and glucose metabolism (section 4) is also important, as glucose intolerance, diabetes and hyperlipidaemia are additional risk factors that are frequently present in the hypertensive population.

The tablet formulations intended for marketing have been shown to be bioequivalent to the gelatin capsule formulations used in pivotal clinical trials, and offer the convenience of single-tablet administration of a combination therapy, with potential compliance benefits. These fixed-dose formulations are now approved in Germany for the treatment of hypertension in patients with BP not adequately controlled with lercanidipine[49] or enalapril[50] alone.

Disclosure

During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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