ADIS DRUG EVALUATION

Drugs 2003; 63 (22): 2449-2472
0012-6667/03/0022-2449/$33.00/0

Lercanidipine

A Review of its Efficacy in the Management of Hypertension

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Data Selection

Sources: Medical literature published in any language since 2000 on lercanidipine, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'lercanidipine'. EMBASE search terms were 'lercanidipine' or 'Rec 15/2375'. AdisBase search terms were 'lercanidipine' or 'Rec 15/2375'. Searches were last updated 02 October 2003.

Selection: Studies in patients with mild-to-moderate or severe hypertension who received lercanidipine. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Lercanidipine, hypertension, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Lercanidipine (Zanidip®) is a vasoselective dihydropyridine calcium channel antagonist that causes systemic vasodilation by blocking the influx of calcium ions through L-type calcium channels in cell membranes. It is a highly lipophilic drug that exhibits a slower onset and longer duration of action than other calcium channel antagonists. Furthermore, lercanidipine may have antiatherogenic activity unrelated to its antihypertensive effect.

In two large, nonblind, noncomparative studies involving approximately 16 000 patients with mild-to-moderate hypertension, systolic blood pressure (BP) [SBP] and diastolic BP (DBP) were significantly reduced after 12 weeks' treatment with lercanidipine 10–20 mg/day. Furthermore, in the largest study, 64% of patients were responders (DBP <90mm Hg) after 12 weeks of treatment and an additional 32% had their BP normalised (BP <140/90mm Hg).

In comparative trials, lercanidipine 10–20 mg/day was as effective as nifedipine slow release (SR) 20–40mg twice daily, amlodipine 10 mg/day, felodipine 10–20 mg/day, nifedipine gastrointestinal therapeutic system (GITS) 30–60mg once daily or verapamil SR 240 mg/day at reducing SBP and DBP in patients with mild-to-moderate hypertension after 2–16 weeks of therapy. In addition, 4 weeks of lercanidipine therapy (10 mg/day) was as effective as captopril 25mg twice daily, atenolol 50 mg/day or hydrochlorothiazide 12.5 mg/day.

Lercanidipine 5–30 mg/day effectively decreased BP in elderly patients (aged >60 years) with mild-to-moderate hypertension or isolated systolic hypertension to the same extent as amlodipine 5–10 mg/day, nifedipine GITS 30–60 mg/day or lacidipine 2–4 mg/day after 24–26 weeks of therapy. In addition, a limited number of studies suggest that lercanidipine may have antihypertensive efficacy in patients with severe or resistant hypertension, in hypertensive patients with type 2 diabetes mellitus and in postmenopausal women with mild-to-moderate essential hypertension.

Lercanidipine is well tolerated, with most treatment-emergent events related to vasodilation. Common adverse events included headache, flushing and peripheral oedema. Importantly, the incidence of vasodilatory oedema was significantly lower in patients receiving lercanidipine than in those receiving some other calcium channel antagonists.

Conclusion: Once-daily lercanidipine is an effective and well tolerated antihypertensive agent in patients with mild-to-moderate hypertension. Furthermore, in a small number of studies, the drug has demonstrated efficacy in patients with severe or resistant hypertension (as add-on therapy), in the elderly and in patients with type 2 diabetes. Importantly, lercanidipine appears to be as effective and at least as well tolerated as many other calcium channel antagonists, but with a decreased incidence of oedema. Limited studies also suggest that this drug can be used in combination therapy. Lercanidipine is therefore an appropriate option for the treatment of patients with mild-to-moderate essential hypertension.

Pharmacodynamic Properties

Lercanidipine is a third-generation dihydropyridine calcium channel antagonist, that blocks calcium entry into smooth muscle cells, thereby causing peripheral vasodilation and a reduction in blood pressure (BP).

The antihypertensive effect of lercanidipine is gradual in onset and long in duration (mean time to equilibrium effect was 70–116 minutes at $\log^{-7}$ to $\log^{-10}$ concentrations). Significant reductions in BP were maintained over a 24-hour period in patients with essential hypertension who received lercanidipine 10 or 20 mg/day.

Lercanidipine is vasoselective and has little cardiodepressant activity. Heart rate or electrocardiographic parameters were not significantly altered in clinical trials in patients with hypertension. In small studies, left ventricular mass was significantly reduced compared with baseline in patients with hypertension treated with lercanidipine 10 mg/day for up to 12 months.

Lercanidipine has an antiatherogenic effect unrelated to its antihypertensive activity. Studies in patients with hypertension with or without type 2 diabetes mellitus have shown that lercanidipine also has antioxidant activity. Lercanidipine 10 mg/day for 16 weeks significantly reduced low-density lipoprotein cholesterol oxidation in patients with hypertension and type 2 diabetes.

Lercanidipine appears to neutrally or favourably affect lipid and glucose metabolism in patients with hypertension. As with other calcium channel antagonists, no significant effect on the albumin/creatinine ratio was seen in patients with hypertension and type 2 diabetes treated with lercanidipine for 16 weeks. In addition, creatinine clearance, but not plasma creatinine concentrations, increased by 10% compared with baseline in patients with chronic renal failure.

Pharmacokinetic Properties

Lercanidipine is administered as a racemic mixture. The mean maximum plasma concentration (C_{max}) of *S*-lercanidipine after a single oral dose of lercanidipine 10 or 20mg in patients with mild-to-moderate hypertension was 1.75 and 4.09 μg/L and time to C_{max} was 2.3 and 3.3 hours; the corresponding mean area under the plasma concentration-time curve (AUC) was 4.55 and 16.36 μg • h/L indicating a non-linear profile. Lercanidipine is highly bound to plasma proteins (>98%).

After absorption, oral lercanidipine undergoes extensive first-pass metabolism, with approximately equivalent amounts of an oral dose eliminated in the urine and the faeces as metabolites. In patients with hypertension or angina pectoris, the mean terminal elimination half-life in plasma for a single oral dose of lercanidipine 10 or 20mg was 8 or 10.5 hours.

The pharmacokinetic profile of lercanidipine in elderly patients or patients with mild hepatic impairment or mild-to-moderate renal impairment is not significantly different from that of otherwise healthy patients with hypertension. How-

ever, accumulation of lercanidipine occurred after repeat administrations in patients with severe renal impairment.

Coadministration of lercanidipine with inhibitors of the cytochrome P450 (CYP) 3A4 (e.g. ketoconazole) led to significantly increased lercanidipine C_{max} (8-fold) or AUC values (15-fold). Furthermore, *in vivo* coadministration of lercanidipine and midazolam, a substrate of CYP3A4, did not alter the plasma concentrations of midazolam, but increased the extent (by ≈40%) and decreased the rate (by ≈75%) of lercanidipine absorption.

No clinically significant interactions were reported when lercanidipine 10 or 20 mg/day was coadministered with β-methyldigoxin, cimetidine at standard dosages, simvastatin 40mg, sildenafil, warfarin, diuretics or ACE inhibitors.

Therapeutic Efficacy

Systolic BP (SBP) was significantly reduced from baseline by 19 and 26mm Hg and diastolic BP (DBP) by 13 and 15mm Hg after 12 weeks of therapy with lercanidipine 10–20 mg/day in two large noncomparative studies involving 16 105 patients with grade 1, 2 or 3 hypertension. Reductions in BP were similar in those receiving lercanidipine monotherapy and those receiving combination therapy with other antihypertensive agents in one trial. Furthermore, in one study (ELYPSE [Eficacia de Lecanidipino y su Perfil de Seguridad]) 64% of patients were responders (DBP <90mm Hg) after 12 weeks of treatment and 32% had their BP normalised (BP <140/90mm Hg).

Compared with other calcium channel antagonists, lercanidipine 10–20 mg/day was as effective as nifedipine slow release (SR) 20–40mg twice daily, amlodipine 10 mg/day, felodipine 10–20 mg/day, nifedipine gastrointestinal therapeutic system (GITS) 30–60mg once daily or verapamil SR 240 mg/day at reducing SBP and DBP in patients with mild-to-moderate hypertension after 2–16 weeks of therapy. Furthermore, 4 weeks of lercanidipine therapy (10 mg/day) was also as effective as captopril 25mg twice daily, atenolol 50 mg/day or hydrochlorothiazide 12.5 mg/day at reducing BP in patients with mild-to-moderate hypertension. Normalisation rates were higher at completion of therapy than after 4 weeks in studies which employed dosage titration in nonresponders after 4 weeks.

In one study, lercanidipine monotherapy reduced BP in patients with severe hypertension, albeit at dosages higher than those currently recommended. As add-on therapy, lercanidipine 10–30 mg/day was as effective as nitrendipine 10–30 mg/day in patients with hypertension not responding to therapy with other antihypertensive agents.

Lercanidipine 5–30 mg/day decreased BP in elderly patients (aged >60 years) with mild-to-moderate hypertension or isolated systolic hypertension to a similar extent to amlodipine 5–10 mg/day, nifedipine GITS 30–60 mg/day or lacidipine 2–4 mg/day after 24–26 weeks of therapy.

Lercanidipine has also demonstrated antihypertensive efficacy in patients with type 2 diabetes and in postmenopausal women with mild-to-moderate essential hypertension in single studies.

Tolerability

Lercanidipine was well tolerated in clinical trials with most treatment-emergent adverse events related to vasodilation. In the two largest studies, involving 16 105 patients with mild-to-moderate hypertension, adverse events were observed in 1.6 and 6.5% of patients receiving lercanidipine 10 or 20 mg/day. Headache (0.2% and 2.9%), ankle oedema (0.4% and 1.2%) and flushing (1.0% and 1.1%) were the most commonly reported events.

Adverse events were reported in 11.8% of lercanidipine recipients (10 or 20mg once daily) compared with 7.0% of those receiving placebo in a pooled analysis of data from 20 clinical trials involving almost 1800 patients with hypertension. Similar percentages of patients withdrew because of poor tolerability (5% and 3%) and the most commonly reported events were headache, flushing, vertigo, palpitations and ankle oedema.

Lercanidipine was well tolerated in elderly patients (aged >60 years) during both short-term (8–24 weeks) and longer-term treatment (>6 months). Adverse events, including peripheral oedema, elevated liver enzymes, flushing and headache were reportedby <3–19.4% of elderly patients receiving lercanidipine 10 or 20 mg/day. A small number of elderly lercanidipine recipients withdrew because of poor tolerability.

Lercanidipine 10 or 20 mg/day showed a similar tolerability profile to captopril 50–100 mg/day, atenolol 50–100 mg/day and losartan 50–100 mg/day. However, adverse events were less common with lercanidipine 10–20mg once daily than with nitrendipine (10 or 20 mg/day), nifedipine SR (20–40 mg twice daily) and nifedipine GITS (30–60 once daily) during 8–24 weeks of therapy. The incidence of peripheral oedema was significantly lower during treatment with lercanidipine 10–20 mg/day than during treatment with amlodipine or nifedipine GITS, whereas treatment withdrawals due to peripheral oedema were similar in patients treated with lercanidipine 10–20 mg/day or lacidipine 2–4 mg/day.

Furthermore, patients reported significantly fewer adverse events after switching to lercanidipine from amlodipine, nifedipine GITS, felodipine or nitrendipine. The incidence of oedema was reduced by 46%, flushing by 51% and headache and rash both by 53% ($p < 0.001$ for all comparisons).

Dosage and Administration

Oral lercanidipine is approved for the treatment of mild-to-moderate hypertension in most of Europe (including the UK), Asia, Australasia and South America. UK prescribing information indicates that lercanidipine therapy should be initiated at 10 mg/day. The dosage can be gradually titrated to 20 mg/day in patients who do not respond satisfactorily.

Dosage adjustments are not required in the elderly or in patients with mild-to-moderate renal or hepatic dysfunction. Lercanidipine is not recommended for use in patients with severe hepatic or renal dysfunction, nor in patients aged <18 years.

Lercanidipine is contraindicated during pregnancy and lactation, in women of child-bearing potential unless effective contraception is used, in patients with left ventricular outflow tract obstruction, untreated congestive heart failure, unstable angina pectoris or within 1 month of a myocardial infarction.

Lercanidipine should not be coadministered with inhibitors of CYP3A4 or cyclosporin or grapefruit juice. Furthermore, caution should be exercised when administering lercanidipine with inducers or other substrates of CYP3A4. Ler-

canidipine can be coadministered with warfarin, simvastatin, β-methyldigoxin and low dosages of cimetidine (≤800 mg/day), although patients receiving concomitant digoxin should be monitored for digoxin toxicity.

1. Introduction

Elevated blood pressure (BP) is a significant risk factor for cardiovascular disease.[1] Indeed, for individuals aged 40–70 years, the risk of myocardial infarction, heart failure, stroke or kidney disease doubles for every 20/10mm Hg increase in systolic/diastolic BP (SBP/DBP). Despite this, up to 20% of people in Western society develop hypertension, and BP is controlled in fewer than 30% of these.[2-4]

Calcium channel antagonists are widely used for the treatment of hypertension, and clinical trials indicate that they are particularly effective when used in combination with other agents.[3] Lercanidipine (Zanidip®[1]) is a highly lipophilic third generation dihydropyridine (DHP) calcium channel antagonist. Its use in the management of hypertension has been reviewed previously in *Drugs*.[5] Since then, lercanidipine has been the subject of further clinical research and these studies are the focus of this review.

2. Overview of Pharmacodynamic Properties

The pharmacodynamic effects of lercanidipine have been evaluated *in vitro*, in animal models and in patients with essential hypertension with or without diabetes mellitus. The main pharmacodynamic properties of lercanidipine are presented in table I.

2.1 Mechanism of Action

Lercanidipine competitively binds to the DHP site of L-type calcium channels in cardiac and vascular smooth muscle cells, inhibiting transmembrane influx of calcium ions and producing muscle relaxation.[6,7,11] As for other DHPs administered as a racemic mixture, the antihypertensive activity of lercanidipine is primarily attributed to the *S*-enantiomer which has 100- to 200-fold greater affinity than the *R*-enantiomer for the L-type calcium channel.[7]

Consistent with its high lipophilicity (log P = 6.0–6.1),[13] lercanidipine is membrane soluble and is taken up into, and stored within, the hydrophobic compartment of the phospholipid bilayer of cell membranes. This property was confirmed by the persistent inhibition of the contractile response to K^+ in rat aorta after repeated washouts,[6,11] and accounts for the gradual onset and long duration of its antihypertensive action observed in *in vitro* studies (section 2.3).

The antihypertensive effect of lercanidipine results from peripheral vasodilation and decreased total peripheral resistance as demonstrated in canine models (section 2.3). [8,10]

2.2 Vascular Selectivity

In vitro data suggest that lercanidipine, unlike other DHP calcium angatonists, is highly selective for the vascular smooth muscle over other smooth muscle types.[11,41] The relaxant potency of lercanidipine in rat aorta was 177-fold higher than in the rat bladder and 8.5-fold higher than in the rat colon.[11,41] In contrast, nitrendipine had similar activity in the three different tissues tested.[11] Also, the ratio of IC_{50} values (concentration required to inhibit contraction by 50%) in cardiac : vascular tissue was higher with lercanidipine (730) than with lacidipine (193), amlodipine (95), felodipine (6) or nitrendipine (3).[12]

Consistent with its vasoselectivity, lercanidipine has a weak cardiodepressant (negative inotropic) activity.[11,12,41] Cardiodepressant activity was lower with lercanidipine than with felodipine (531-[12] and 857-fold[11,41]), nitrendipine (426-[12] and

1 Also registered as Lerzam®, Lerdip®, Lercadip®, Zanedip®, Cardiovasc®, Vasodip™, Corifeo™, Carmen™. Use of tradenames is for product identification purposes only and does not imply endorsement.

Table I. Overview of the pharmacodynamic properties of lercanidipine

Mechanism of action
Selectively blocks voltage-dependent calcium influx through L-type channels in SMC membranes[6-9]
Reduces BP via peripheral vasodilation in animal models[8,10]
Highly selective inhibitory effect in vascular tissues *in vitro*[11,12]
Weak cardiodepressant (negative inotropic) activity[11,12]
Antihypertensive effects
Gradula onset and prolonged duration of antihypertensive activity in *in vitro* and *ex vivo* studies[7,11-13]
Lercanidipine 10 or 20 mg/day for 4 wks or 4mo significantly reduces BP over 24h in patients with essential hypertension[14-16]
Trough : peak BP is generally >50% in patients with essential hypertension[14,15]
Cardiovascular effects (in patients with hypertension)
Lercanidipine (10 or 20 mg/day) generally has no clinically significant effects on HR[14,16-24]
Lercanidipine 10 or 20 mg/day for up to 16 wks has no significant effects on ECG parameters[14,17,18,20-22]
Lercanidipine 10 mg/day for 6–12mo significantly reduces LVM from baseline (p-values not reported).[24-26] Lercanidipine 10 mg/day reduces LVM to a similar extent to hydrochlorothiazide 25 mg/day[24] or enalapril (dosage not reported)[25] but significantly more than losartan 50 mg/day ($p < 0.05$) after 6–12mo[26]
Antiatherogenic effects
In vitro, lercanidipine 10–50 μmol/L dose-dependently inhibits arterial SMC proliferation and migration[27]
Lercanidipine has antioxidant activity in patients with hypertension with[28] or without[29,30] type 2 diabetes mellitus
Reduces atherosclerotic lesions in hypercholesterolaemic rabbits[31]
Renal effects
Causes dilation of both the afferent and efferent glomerular arterioles in SHR[32]
Inhibits glomerular hypertrophy, decreases the volume of the glomerular tuft and improves the morphology of convoluted tubules in SHR[32,33]
Prevents increases in urine volume and urinary albumin concentrations in SHR.[33] May reduce proteinuria in subtotally nephrectomised SHR[34]
Metabolic effects
Lercanidipine 10–30 mg/day for 24–48 wks did not significantly alter the serum concentrations of TC, HDL-C, LDL-C, triglycerides or apolipoproteins A-I and B in patients with hypertension with[29] or without[35] type 2 diabetes
Lercanidipine 10 or 20 mg/day for 8 wks significantly reduces fasting blood glucose levels, HbA_{1c} and serum fructosamine from baseline ($p < 0.001$) and improves oral glucose tolerance ($p < 0.001$) in patients with hypertension and concomitant type 2 diabetes[36]
Other effects
Causes less peripheral oedema than nifedipine[37] or amlodipine[38] in patients with mild-to-moderate hypertension (section 5.1)
Reduces the incidence of cerebral stroke in salt-fed SHR[39] and has a protective effect in the brain in SHR[40]

BP = blood pressure; **ECG** = electrocardiograph; **HbA_{1c}** = glycosylated haemoglobin A_{1c}; **HDL-C** = high-density lipoprotein cholesterol; **HR** = heart rate; **LDL-C** = low-density lipoprotein cholesterol; **LVM** = left ventricular mass; **SHR** = spontaneously hypertensive rats; **SMC** = smooth muscle cell; **TC** = total cholesterol.

667-fold[11,41]), lacidipine (12.5-fold)[12] and amlodipine (4.4-fold)[12] in rabbit ventricle *in vitro*, and negative inotropism was documented for nifedipine, but not lercanidipine *in vivo* in rabbits.[42]

2.3 Antihypertensive Effects

Lercanidipine has a gradual onset and a long-lasting antihypertensive effect, despite its short plasma half-life (section 3.2), as shown in numerous *in vitro* and *ex vivo* studies that demonstrated that lercanidipine reduced contractions in isolated rat aortic strips,[7,11] stimulated isolated rabbit aorta[12] and human subcutaneous arteries.[13] Furthermore, the antihypertensive activity of lercanidipine has been demonstrated *in vivo* in spontaneously hypertensive rats (SHR) and dogs.[8,10] The gradual onset and prolonged duration of action (mean time to equilibrium effect was 70–116 minutes at $\log^{-7}$ to $\log^{-10}$ concentrations) was significantly correlated with its high degree of lipophilicity ($p < 0.05$).[13]

BP reductions persisted over 24 hours, as assessed using ambulatory blood pressure monitoring (ABPM), after a single dose of lercanidipine 10[16]

or 20mg[14] in patients with mild-to-moderate hypertension.

2.4 Cardiovascular Effects

Levels of specific markers of sympathetic activation (heart rate, plasma norepinephrine and muscle sympathetic nerve traffic) that were increased from baseline to a similar extent after a single dose of lercanidipine 10 mg/day or felodipine 10mg (both $p < 0.01$) returned to baseline after 8 weeks treatment with lercanidipine but not with felodipine.[43] Furthermore, in a well designed trial involving 60 patients with essential hypertension, plasma norepinephrine levels were significantly increased by nifedipine gastrointestinal therapeutic system (GITS) 30–60 mg/day ($p < 0.05$) but not by lercanidipine 10–20 mg/day during 48 weeks of treatment, suggesting that sympathetic activation occurs during therapy with nifedipine gastrointestinal therapeutic system (GITS) but not with lercanidipine.[44]

There were no significant changes in electrocardiographic (ECG) parameters with lercanidipine treatment (10 or 20 mg/day for 2–16 weeks) in noncomparative[14,22] and comparative[17,18,20,21,45-47] clinical trials in patients with mild-to-moderate or severe essential hypertension. Heart rate was generally not affected by lercanidipine therapy (section 5) and the number of patients displaying ventricular and/or supraventricular cardiac arrhythmias at baseline did not change significantly after 2 weeks' treatment with lercanidipine.[17] In contrast, one large, noncomparative study ($n = 9059$) reported a small but significant reduction in BP after 1 and 3 months of treatment with lercanidipine 10 mg/day ($p < 0.001$ for both vs baseline).[48]

Lercanidipine 10 mg/day for 12 months significantly reduced left ventricular hypertrophy compared with the angiotensin II receptor inhibitor losartan 50 mg/day in 54 patients with mild-to-moderate hypertension and concomitant type 2 diabetes ($p < 0.05$) as measured using ECG evaluation.[26] Limited data from two studies suggest that lercanidipine (10 mg/day or dosage not reported) for 6–12 months reduces left ventricular mass in patients with essential hypertension to a similar extent to hydrochlorothiazide 25 mg/day[24] or enalapril (dosage not reported).[25]

2.5 Antiatherogenic Effects

Lercanidipine, like other calcium channel antagonists, has a potential antiatherogenic effect unrelated to its antihypertensive activity.[27-31,49] Lercanidipine 10–50 μmol/L inhibited arterial smooth muscle cell proliferation and migration in a dose-dependent manner *in vitro*[27] and reduced the extent of atherosclerotic lesions in hypercholesterolaemic rabbits.[31]

Studies in patients with hypertension with[29] or without[28,30] type 2 diabetes have shown that lercanidipine also has antioxidant activity. Lercanidipine 10 mg/day for 16 weeks significantly reduced low-density lipoprotein cholesterol (LDL-C) oxidation in patients with hypertension and diabetes ($p < 0.001$ vs baseline) to a similar extent to losartan 50 mg/day.[29]

2.6 Metabolic Effects

Lercanidipine appears to neutrally or favourably affect lipid metabolism in patients with essential hypertension[35] and those with type 2 diabetes and mild-to-moderate hypertension.[29] In randomised, double-blind[35] or single-blind[29] studies, lercanidipine (10–30 mg/day for 24–48 weeks) did not significantly alter the serum concentrations of total cholesterol, high-density lipoprotein cholesterol (HDL-C), LDL-C, triglycerides or apolipoproteins A-I and B in patients with hypertension,[35] and neither lercanidipine 10 mg/day nor losartan 50 mg/day for 16 weeks significantly changed the lipid profile in patients with hypertension and type 2 diabetes.[29]

In contrast, in patients with hypertension, lercanidipine 10 mg/day for 6 months decreased levels of total cholesterol, LDL-C and triglycerides (all $p < 0.001$) in one study[50] and reduced total cholesterol levels in another ($p < 0.00005$)[51] [both reported as abstracts].

Lercanidipine may improve the glucose profile in patients with hypertension and concomitant type 2 diabetes, but this requires confirmation from more

extensive clinical experience.[36] Lercanidipine 10 or 20 mg/day for 8 weeks reduced fasting blood glucose, glycosylated haemoglobin A_{1c} and serum fructosamine levels from baseline (all $p < 0.001$) and improved oral glucose tolerance in one study ($p < 0.001$).[36] In additional studies, lercanidipine 10 mg/day had no effect on haemoglobin A_{1c} levels during 16 weeks of therapy,[29] but significantly reduced blood glucose levels ($p < 0.00005$) after 6 months.[51]

2.7 Renal Effects

Lercanidipine appears to have a nephroprotective effect in SHR.[33,52] The drug may improve glomerular capillary pressure, as vasodilation of both the afferent and efferent glomerular arterioles was induced in SHR after 12 weeks of treatment.[32] In addition, lercanidipine also inhibited glomerular hypertrophy,[33] decreased the volume of the glomerular tuft [33]and improved the morphology of convoluted tubules in SHR.[52]

Lercanidipine has demonstrated vasodilatory effects on different branches of the renal arterial tree in SHRs.[52] Lercanidipine decreased the narrowing of the arterial lumen, inhibited the thickening of the tunica media, reduced the accumulation of connective tissue within the adventitia and reversed remodelling of renal artery branches in SHR.[33] Additionally, unlike other DHP calcium channel antagonists (manidipine and nicardipine), lercanidipine had a vasodilatory effect on small sized arteries with a diameter <25µm.[52] In branches with a diameter of 50–150µm lercanidipine reversed remodelling to a significantly greater extent ($p < 0.05$) than manidipine or nicardipine.[52]

Increases in urine volume and urinary albumin concentrations were prevented in SHR [33,52] and proteinuria was reduced in subtotally nephrectomised SHR that were administered lercanidipine.[34] These effects, however, have yet to be demonstrated in patients with hypertension.

As with other calcium channel antagonists, no significant effect on the albumin/creatinine ratio was seen in patients with hypertension and type 2 diabetes who were treated with lercanidipine for 16 weeks.[29] To date, clinical trials have demonstrated that lowering BP in patients with diabetes reduces the risk of cardiovascular events and death from nephropathy; however, there is no clear evidence of one class of antihypertensive drug having a greater treatment benefit than another. Indeed, to achieve the target BPs recommended in patients with hypertension and diabetes, drugs from more than one antihypertensive class are generally required.[53]

In an additional study creatinine clearance but not plasma creatinine concentrations increased by 10% compared with baseline ($p = 0.019$) in 175 patients with chronic renal failure (CRF) and BP higher than that recommended for CRF (130/85 mm Hg) [abstract only].[54]

2.8 Other Effects

Despite a similar antihypertensive effect (section 4.1.3) lercanidipine appears to cause less peripheral oedema than nifedipine[37] or amlodipine[38] in patients with hypertension (section 5.1). In randomised, double-blind studies, lercanidipine 10 mg/day produced a smaller increase in pretibial subcutaneous tissue pressure or ankle-foot volume than nifedipine GITS 30 mg/day after 12 weeks (47.1% vs 90.4% and 11.2% vs 21.9%; $p < 0.001$ for both comparisons) [figure 1][37] and less of an increase in leg volume compared with amlodipine 5–10 mg/day after 8 weeks (5.3mL vs 60.4mL; $p < 0.001$) [both measured by water displacement volumetry].[38] In

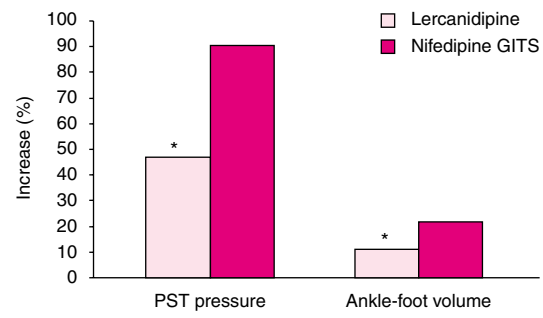

Fig. 1. Mean increase in pretibial subcutaneous tissue (PST) pressure and ankle-foot volume, as measured by water displacement volumetry, in 60 patients with mild-to-moderate hypertension receiving either lercanidipine 10–20 mg/day or nifedipine gastrointestinal therapeutic system (GITS) 30–60 mg/day for 12 weeks in a double-blind, parallel-group study.[37] * $p < 0.01$ vs nifedipine GITS.

Table II. Summary of pharmacokinetic properties of single-dose lercanidipine (LER) in healthy volunteers and patients with mild-to-moderate hypertension[57]

Dosage	C_{max}	t_{max}	AUC	$t_{1/2}$	Elimination of metabolites (%)[a]	
	(μg/L)[b]	(h)[b]	(μg • h/L)[b]	(h)[c]	urine	faeces
LER 10mg	1.75	2.3	4.55	8.0	NR	NR
LER 20mg	4.09	3.3	16.36	10.5	43.8	50.4

a Healthy volunteers received a single dose of [^{14}C]lercanidipine 20mg.

b Plasma concentrations of *S*-lercanidipine were measured.

c Values observed with more sensitive assay in patients with hypertension or angina pectoris.[59]

AUC = area under the plasma concentration-time curve; **C_{max}** = mean maximum plasma concentration; **NR** = not reported; **$t_{1/2}$** = terminal elimination half-life; **t_{max}** = time to C_{max}.

addition, leg weight was increased to a smaller extent with lercanidipine 20 mg/day (37g) than with amlodipine 10 mg/day (80g) after 2 weeks of therapy as measured by plethysmography.[55]

In a prospective multicentre trial 538 patients with hypertension (mean age 60 years) received lercanidipine 10 mg/day (and ramipril 2.5 mg/day if BP was not controlled) for 6 months. No change in anxiety levels was observed during therapy, although psychosomatic semiology significantly improved at the completion of treatment compared with baseline ($p < 0.0005$; both assessed using patient questionaires).[56]

3. Overview of Pharmacokinetic Properties

The pharmacokinetics of lercanidipine have been examined in healthy volunteers and patients with hypertension, including elderly patients and patients with renal or hepatic impairment. Whereas most pharmacokinetic studies have been reported in one review paper (Barchielli et al.[57]), additional information has been obtained from the manufacturer's prescribing information (table II)[58] and another study.[59]

3.1 Absorption and Distribution

Lercanidipine is administered as a racemic mixture of *R*- and *S*-lercanidipine, and after oral administration, it is completely absorbed from the gastrointestinal tract.[57] Absolute bioavailability in fed patients with hypertension is reduced to approximately 10%.[58]

Following oral administration lercanidipine demonstrates nonlinear pharmacokinetics.[57] After administration of a single oral dose of lercanidipine 10, 20 or 40mg (not a recommended dose) the mean maximum plasma concentration (C_{max}) values of *S*-lercanidipine in healthy volunteers were in the ratio 1 : 3 : 8 and the area under the plasma concentration-time curve (AUC) values in the ratio 1 : 4 : 18.[57] In hypertensive patients the exposure after 20 mg once daily for 4 weeks was 2.7-fold higher than that after the 10mg dose.[57]

Once absorbed, lercanidipine accumulates in the lipid bilayer of cell membranes in the arterial wall (section 2.1) and shows high serum protein binding (>98%).[57] The apparent volume of distribution of lercanidipine 2mg was 2–2.5 L/kg after a 15-minute intravenous infusion in healthy volunteers, reflecting the high lipophilicity of the drug.[57]

3.2 Metabolism and Elimination

After absorption, oral lercanidipine undergoes extensive first-pass metabolism to largely inactive metabolites.[57] Lercanidipine is metabolised by the hepatic enzyme cytochrome P450 (CYP) 3A4 and has the potential for interactions with drugs mediated by this pathway (section 3.4).[58] Lercanidipine is eliminated to a similar extent in the urine and faeces, following biotransformation (table II). No unchanged drug was recovered in the urine.[57]

Administration of a single dose of lercanidipine 10 or 20mg to fasting healthy volunteers or patients with hypertension resulted in mean terminal plasma elimination half-lives ($t_{1/2}$) of 2.8 and 4.4 hours.[57] However, with the use of more sensitive assays in

studies in hypertensive patients and in those with angina pectoris, the $t_{1/2}$ for lercanidipine 10 or 20mg was 8.0 or 10.5 hours.[59]. After oral administration of lercanidipine 10 or 20 mg/day for 7 days in patients with mild-to-moderate hypertension, an accumulation factor of approximately 25–30%, consistent with a $t_{1/2}$ of 10 hours was observed.[57]

3.3 Special Populations

The pharmacokinetics of lercanidipine in elderly patients or patients with mild hepatic or mild-to-moderate renal impairment are not significantly different from those in otherwise healthy patients with hypertension[57] and no dosage adjustments are needed for these patients (section 6). However, in patients with severe renal impairment (undergoing regular dialysis), lercanidipine accumulates after repeat administrations (20 mg/day for 7 days).[57] Although no studies have been undertaken in patients with moderate or severe hepatic impairment the bioavailability and antihypertensive effect of the drug may be increased in these patients.[58] Therefore, lercanidipine is not recommended for use in patients with severe renal (creatinine clearance <10 mL/min) or hepatic impairment [section 6].[58]

3.4 Potential for Drug Interactions

Potential drug interactions have been evaluated in studies in patients with hypertension and in healthy volunteers (table III).

Coadministration of drugs or other substances that inhibit or induce CYP3A4 has the potential to influence the pharmacokinetic profile of lercanidipine (table III).[58,60] As a result, the coadministration of lercanidipine and CYP3A4 inhibitors, including grapefruit juice, should be avoided (table III and section 6)[58] and the concomitant administration with cyclosporin is contraindicated (section 6).[58,60] However, fluoxetine (an inhibitor of CYP3A4 and 2D6) did not influence the pharmaco-

Table III. Potential interactions between lercanidipine (LER) and other drugs in patients with hypertension and healthy volunteers (not stated whether studies are single- or multiple-dose)[58,60]a

Concomitant drug	Effect on pharmacokinetics	Clinical recommendation[58]
Ketoconazole	LER: ↑ C_{max} (8-fold); ↑ AUC (15-fold)	Avoid coadministration with inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir, erythromycin, troleandomycin)
Cyclosporin	LER: ↑ plasma levels 3-fold	Coadministration contraindicated
	Cyclosporin: ↑ AUC (21%)	
Fluoxetine	LER: no significant change to pharmacokinetic profile	No dosage adjustment required
Oral midazolam	LER: ↑ absorption (40%); ↓ rate of absorption	No dosage adjustment required
	Midazolam: no change to pharmacokinetic profile	
Metoprolol	LER: ↓ bioavailability (50%)	An increase in the lercanidipine dose may be required when coadministered with β-blockers
	Metoprolol: bioavailability not altered	
Cimetidine	LER: no significant change	Bioavailability and antihypertensive effect of lercanidipine may be increased with cimetidine doses higher than 800 mg/day
Steady-state β-methyldigoxin	LER: no change to pharmacokinetic profile	
Steady-state digoxin	Digoxin: ↑ C_{max} (33%); AUC and renal clearance not significantly altered	Monitor patient for signs of digoxin toxicity
Simvastatin 40mg	LER: AUC not significantly altered	No interaction is expected if lercanidipine is administered in the morning and simvastatin in the evening
	Simvastatin: ↑ AUC (56%)	
	β-hydroxyacid simvastatin: ↑ AUC (28%)	
Warfarin	Warfarin: no changes to the pharmacokinetic profile	

a A LER 20mg dose was coadministered.

AUC = area under the plasma concentration-time curve; **C_{max}** = maximum plasma concentration; **CYP** = cytochrome P450.

kinetics of lercanidipine in elderly volunteers (table III).[58,60]

Coadministration of lercanidipine with inducers of CYP3A4, such as anticonvulsants (e.g. phenytoin, carbamazepine) and rifampicin may enhance lercanidipine metabolism and reduce its antihypertensive activity.[58] Therefore, the combination of lercanidipine and these drugs should be used with caution and the BP monitored more frequently than usual (section 6).[58]

It is also recommended that caution be used when lercanidipine is to be coadministered with other substrates of CYP3A4 (e.g. terfenadine, astemizole, quinidine and class III antiarrhythmic drugs such as amiodarone).[58]

Conversely, lercanidipine does not appear to inhibit the CYP3A4 or CYP2D6 pathways *in vitro* or *in vivo* and does not affect the pharmacokinetics of drugs metabolised by these pathways (inlcuding midazolam and metoprolol).[60,61] However, the extent of absorption of lercanidipine was increased (by approximately 40%) and the rate of absorption decreased (t_{max} was delayed from 1.75 to 3 hours) by coadministration with midazolam.[58] In addition, the bioavailability of lercanidipine was reduced by 50% after coadministration with metoprolol.[58] It may be necessary to increase the dosage of lercanidipine when coadministered with β-adrenoreceptor antagonists, except those that are eliminated unchanged (e.g. atenolol).[58]

Patients receiving concomitant lercanidipine 20mg and steady-state β-methyldigoxin (a pro-drug of digoxin) did not demonstrate any drug interactions (table III).[57,60] However, healthy volunteers given lercanidipine 20mg followed by digoxin (0.25mg) demonstrated a mean increase in digoxin C_{max} (33%) [table III].[58] Patients receiving concomitant lercanidipine and digoxin should therefore be monitored closely for signs of digoxin toxicity.[58]

No clinically significant interactions were reported when lercanidipine 10 or 20 mg/day was coadministered with cimetidine at standard dosages,[60] simvastatin 40mg,[58] sildenafil,[62] warfarin,[58] diuretics[58] or ACE inhibitors[58] (table III).

4. Therapeutic Efficacy

The efficacy of lercanidipine has been evaluated in noncomparative[48,56,63-65] and comparative studies.[15,17-21,35,37,45-47,55,66-68] Trials primarily involved patients with mild-to-moderate hypertension, generally defined as DBP 95–115mm Hg after a 2- to 4-week placebo run-in period (although BP limits varied in some studies[15,37,48,68]). Three additional studies have investigated the effects of lercanidipine in patients with severe (DBP ≥110mm Hg)[22] or resistant (DBP 100–119mm Hg)[69,70] hypertension and one study performed a subgroup analysis in patients with type 2 diabetes and hypertension.[36]

In most trials, patients were aged 18–75 years (mean age 48–63 years) years, although one trial specifically examined the effects of lercanidipine in postmenopausal women, and six other studies investigated the effect of the drug in elderly patients (aged >60 or >65 years) with mild-to-moderate essential[64-68] or isolated systolic (SBP ≥160mm Hg and DBP <95mm Hg) hypertension (section 4.4.1).[46]

A washout period of 1–3 weeks prior to the placebo run-in period was used in most studies except those in patients with severe and resistant hypertension (<1 week for ethical reasons).[22,69,70]

With one exception,[68] the starting dosage of lercanidipine was 10 or 20 mg/day in all trials (not reported in one study; available as an abstract).[56] In several studies dosages were increased to 20 or 30 mg/day after 4,[15,18,21,35,37,45,46,66] 8[20,65] or 12[20] weeks in patients not responding to therapy with the lower dose (usually defined as DBP >90mm Hg or reduced by <10mm Hg). In these trials the dosage is identified as lercanidipine 10–20 or 20–30 mg/day etc (although lercanidipine 30 mg/day is not currently approved for use [section 6]). Lercanidipine was administered once daily in all studies and a double-dummy approach was used in comparisons with agents administered twice daily.

Lercanidipine has been evaluated primarily in short-term (2- to 16-weeks) studies, although four longer-term (6- to 24-months) studies[56,65,66,71] have recently been completed. BP reductions after 4 or 8 weeks or at completion of therapy were the primary endpoints in most studies of mild-to-moderate hy-

pertension. Secondary endpoints included the number of patients responding to therapy (DBP < 90mm Hg or reduction of ≥10mm Hg) and the number of patients with normalised BP (DBP ≤90mm Hg or BP <140/90). Where stated, BP was measured either sitting or in the supine position ≈24 hours after the last dose (trough). Exclusion criteria included secondary hypertension, cardiovascular disease, renal or hepatic dysfunction and SBP >220mm Hg.

4.1 Mild-to-Moderate Hypertension

4.1.1 Noncomparative Studies

DBP and SBP were reduced by lercanidipine 10–20 mg/day in two large noncomparative 12-week studies.[48,63] The ELYPSE (Eficacia de Lecanidipino y su Perfil de Seguridad; n = 9059)[48] trial and another study (n = 7046)[63] involved patients with grades 1 or 2 (BP 140–179/90–190mm Hg),[48,63] or grade 3 (>180/>110mm Hg) hypertension.[63] In both trials, most patients (69%[48] and 66%)[63] had previously been treated with at least one other antihypertensive drug. Treatment was changed to lercanidipine (monotherapy[48,63] or in combination with other agents [not specified][63]) because of insufficient efficacy or poor tolerability. In addition, lercanidipine was titrated to the higher dosage of 20 mg/day in 1.8% of patients in one study, but did not specify when the dose was increased (abstract only).[63]

Overall, mean SBP was reduced by 19 and 26mm Hg and mean DBP by 13 and 15mm Hg compared with baseline after 12 weeks of therapy in the two studies ($p < 0.001$ for both SBP and DBP where reported[48]) [table IV]. One study also reported significant reductions in mean SBP and DBP from baseline after 4 weeks ($p < 0.001$).[48] Furthermore, 42.2% of patients in one study received other antihypertensive agents in addition to lercanidipine 10 mg/day throughout the duration of study; reductions in mean BP for these patients were similar to those receiving lercanidipine monotherapy (DBP 26 vs 26mm Hg and SBP 15 vs 14mm Hg) [table IV].[63]

After 4 and 12 weeks of treatment in the ELYPSE study, 50% and 64% of patients responded to therapy and 32% had normalised BP levels (<140/90mm Hg) at the completion of therapy (table IV).[48]

Similarly, in a third study (ZANYCAL [acronym not defined]), available as an abstract only, 1208 patients with essential hypertension received lercanidipine (dosage not reported) for 6 months with enalapril 20 mg/day added after 1 month if BP was not adequately controlled (38% of patients).[56]

Table IV. Efficacy of once-daily lercanidipine (LER) as monotherapy[48,56,63] or in combination with other antihypertensives[56,63] in patients (pts) with mild-to-moderate hypertension in three nonblind, noncomparative studies of 3-[48,63] or 6-[56] months duration. Blood pressure (BP) reduction was the primary endpoint in all studies

Reference	Patient age (mean) [y]	No. of pts evaluated	Starting dosage (mg/day)	Mean SBP/DBP (mm Hg) baseline	4 wks	endpoint	Normalised BP at endpoint[a] (% patients)
Barrios et al.[48]	(63)	9059	LER 10	160/96	147*/86*	141*/83*	32
Guillen et el.[56]		749	LER (dosage not reported)	160/94		135/81	72[b]
		459	LER (dosage not reported) + ENL 20	160/94		135/81	61[b]
Schwinger and Schmidt-Mertens[63][c]	14–96	4070	LER 10	165/98		139/83	
		2976	LER 10 + CT[d]	169/98		143/84	

a BP <140/90mm Hg.

b No. of pts who attained BP control (not defined in abstract).

c Abstract. 34% of pts were aged >65 years and 1.8% of pts received LER 20 mg/day (abstract does not report whether these pts received monotherapy or CT). 13% of pts had severe hypertension.

d Pts received LER + CT (undefined in abstract).

CT = combined therapy; **DBP** = diastolic BP; **ENL** = enalapril; **SBP** = systolic BP; * $p < 0.001$ vs baseline.

Mean SBP and DBP were reduced by 25 and 13.5mm Hg in the overall group after 6 months, and the percentage of patients attaining BP control was higher in those receiving lercanidipine monotherapy than those receiving combination therapy (72% vs 61%; table IV) [BP control not defined and significance not reported].[56]

4.1.2 Comparisons with Other Calcium Channel Antagonists

In double-blind and crossover design studies, lercanidipine 10–20 mg/day was as effective as nifedipine slow release (SR) 20–40mg twice daily,[45] nifedipine GITS 30–60mg once daily,[37,47] amlodipine 10 mg/day,[19,55] felodipine 10–20 mg/day[47] and verapamil SR 240 mg/day[17] at reducing SBP and DBP in patients with mild-to-moderate hypertension after 2–16 weeks of therapy (table V).

Furthermore, ABPM during the 24 hours following administration showed that reductions in mean peak DBP were at least as great with lercanidipine 10 mg/day (18mm Hg) as with nifedipine SR 20mg twice daily (18mm Hg), but slightly smaller than with nifedipine GITS 60mg once daily (20mm Hg) after 16 weeks of therapy.[15] Peak reductions in DBP were, however, numerically greater with lercanidipine than with amlodipine 10mg once daily (15mm Hg), verapamil SR 240mg once daily (12mm Hg) and felodipine extended release (ER) 10mg once daily (8mm Hg) [no between group p-values were reported; table V].[15] In contrast, trough reductions in DBP (24 hours after administration) were numerically higher with lercanidipine (15 mm Hg) than with nearly all other calcium channel antagonists investigated (4–13mm Hg) [significance not reported]. [15] Reductions in trough SBP were also similar with lercanidipine (16mm Hg) and the other calcium channel antagonists (13–17mm Hg).[15]

BP normalisation rates in patients receiving lercanidipine were 72%[47] and 89%[45] in two studies at 4 weeks and ranged from 56–89% at endpoint in trials of 2–16 weeks duration (table V).[17,19,45,47] Studies in which the lercanidipine dosage was titrated from 10 to 20 mg/day after 4 weeks in nonresponder patients observed that normalisation improved after titration to higher dosages in all treatment groups.[37,45]

4.1.3 Comparisons with Other Antihypertensives

Four weeks of treatment with lercanidipine 10mg once daily was as effective as captopril 25mg twice daily,[18] atenolol 50 mg/day[21] and hydrochlorothiazide (HCTZ) 12.5 mg/day[35] at reducing BP in patients with mild-to-moderate hypertension in three well designed studies (table VI). Reductions in mean BP (versus baseline) were also similar at the completion of therapy (12–24 weeks) with lercanidipine (SBP/DBP 18–23/11–25mm Hg) and all other antihypertensives tested including losartan (BP 19–21/11–20mm Hg; table VI) [each treatment group included patients who remained on the starting dosage and those in whom dosage was titrated to effect].[18,20,21,35]

In all treatment groups, the number of responder and normalised patients increased after nonresponding patients received a higher titrated dosage.[18,20,21,35] Titration to the higher lercanidipine dosage (20 mg/day) was required in 4%,[35] 25%,[18] 28%[21] and 44%[20] of patients at weeks 4,[18,21,35] 8[20] or 12,[20] and similar rates of titration were required in patients receiving HCTZ (4%),[35] captopril (25%),[18] atenolol (18%)[21] and losartan (40%)[20] in the same studies. Furthermore, in several studies the proportion of normalised patients was 71–100% in the lercanidipine group and 65–96% in other treatment groups after 12–24 weeks of therapy (table VI).[18,20,21,35]

4.2 Severe Hypertension

The efficacy of lercanidipine in patients with severe hypertension (DBP ≥110mm Hg) has been evaluated in only one small, randomised, nonblind study (n = 50);[22] other trials included such patients but did not provide separate results for this subgroup.[63,72] Briefly, lercanidipine 20–40 mg/day significantly reduced mean DBP by approximately 22 and 29mm Hg in patients with severe essential hypertension after 30 and 60 days of therapy ($p < 0.001$ for both periods) [only lercanidipine 10 and 20 mg/day are approved for use; section 6].[22] Almost all patients receiving lercanidipine 20–40 mg/

Table V. Efficacy of lercanidipine (LER), compared with other calcium channel antagonists, in randomised studies involving patients (pts) aged 18–74 years (mean age 48–58 years) with mild-to-moderate hypertension.[a] Where reported, primary endpoints were absolute reductions in blood pressure (BP) at 2,[17] 4[19,45] or 12 weeks,[37] reduction during the 24h period following administration for 2 or 4 months,[15] or reduction in leg oedema[55]

Reference (study design)	Duration of therapy	No. of pts evaluated	Starting dosage[b] (titrated dosage in NR pts)[d] [mg]	Mean SBP/DBP (mm Hg)[c]			Normalised BP at endpoint[e] (% patients)
				baseline	4w	endpoint	
Cavallini and Terzi[17] (db, pg)	2w	16	LER 20	160/101		151*/93*	56
		18	VER SR 240	153/99		141*/91*	72
De Giorgio et al.[19] (db, co)	4w	16	LER 20	161/99		143**/89**[f]	33 (1st period)
							86 (2nd period)
		16	AML 10	158/99		149**/88**[f]	86 (1st period)
							56 (2nd period)
Fogari et al.[37] (db, pg)	12w	30	LER 10 (20)	163/98		144***/86***	
		30	NIF GITS 30 (60)	162/97		143***/86***	
Macchiarulo et al.[15] (nb, co)	4mo	15	LER 10	155/101		139†/78†[g]	
		20	NIF SR 20 bid	150/100		133†/83†[g]	
		20	NIF GITS 60	150/105		129†/85†[g]	
		20	AML 10	148/105		129†/90†[g]	
		15	FEL ER 10	152/98		139/90[g]	
		20	VER SR 240	150/96		135†/84†[g]	
Pedrinelli et al.[55][h] (nb, co)	2w	22	LER 20	145/92		137**/83**	
		22	AML 10	147/94		137**/83**	
Policicchio et al.[45]	16w	57	LER 10 (20)	163/101	151***/91***	144/84[i]	89[i]
(db, dd, pg, mc)		59	NIF 20 (40) bid	163/101	151***/91***	140/82[i]	98[i]
Romito et al.[47] (db, pg, mc)	8w	89	LER 10 (20)	155/99	142**/88**	141**/87**	72[i]
		79	FEL 10 (20)	155/99	140**/85**	138**/85**	74[i]
		82	NIF GITS 30 (60)	155/99	143**/88**	142**/86**	70[i]

a DBP 95–115mm Hg,[17,19,45] 95–109 mm Hg[47] or 90–110 mm Hg.[15,37,55]

b Dosages were once daily unless specified otherwise.

c With three exceptions in which patients were seated and/or standing,[17,37,47] all BP measurements are supine values.[15,19,45,55]

d Dosage titrated after 4w if DBP >90mm Hg or DBP reduced by <10mm Hg.

e DBP ≤90mm Hg.

f Value is the mean of both treatment periods.

g Values are mean peak BP reduction, after 2mo of treatment.

h Abstract.

i Values estimated from graph.

AML = amlodipine; **bid** = twice daily; **co** = crossover; **db** = double-blind; **DBP** = diastolic BP; **dd** = double dummy; **ER** = extended release; **FEL** = felodipine; **GITS** = gastrointestinal therapeutic system; **mc** = multicentre; **NIF** = nifedipine; **nb** = nonblind; **NR** = nonresponders; **pg** = parallel group, **SBP** = systolic BP; **SR** = slow release; **VER** = verapamil; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs baseline; † $p < 0.01$ vs baseline during the 24-hr period following administration.

Table VI. Efficacy of lercanidipine (LER), compared with that of antihypertensives other than calcium channel antagonists in randomised, double-blind, parallel-group studies. Patients (pts) were aged 18–75 years (mean age 55–58 years) with mild-to-moderate hypertension (diastolic blood pressure [DBP] 95–115mm Hg). The primary endpoint was blood pressure (BP) reduction at 4 weeks in three studies[18,21,35] and not specified in the other study[20]

Reference	Duration of therapy (wks)	No. of pts evaluated	Starting dosage[a] (titrated dosage in NR pts)[d] [mg]	Mean SBP/DBP (mm Hg)[b] baseline	4 wks	endpoint	Normalised BP[c] (% patients) 4 wks	endpoint
Barbagallo	12	52	LER 10 (20–30)	161/100	147*/89*	138/80[e,f]	97[e]	81[e]
Sangiorgi et al.[18]		57	CAP 25 (37.5–50) bid	159/100	148*/91*	140/80[e,f]	93[e]	74[e]
James et al.[20]	16	234	LER 10 (20)	166/102		148/91[f]		71
		231	LOS 50 (100)	165/103		144/92[f]		65
Morisco and Trimarco[21]	16	102	LER 10 (20)	157/100	145*/90*	138/75[e,f]	65	80
		102	ATE 50 (100)	157/100	142*/88*	138/84[e,f]	76	86
Notarbartolo et al.[35]	24	26	LER 10 (20)	159/105	143*/92*	139/84[f,g]	54	100
		26	HCTZ 12.5 (25)	158/103	146*/93*	138/84[f,g]	54	96

a Administration was once daily unless otherwise indicated.

b Where reported, all BP measurements are supine values (position not reported in one study[18]).

c DBP ≤90mm Hg.

d Dosage titrated after 4[18,21,35] or 8–12w[20] if DBP >90mm Hg or DBP reduced by <10mm Hg.

e Value estimated from graph.

f p-Values not reported.

g Values were obtained at 8w and did not change significantly during the remainder of the study.

ATE = atenolol; **bid** = twice daily; **CAP** = captopril; **HCTZ** = hydrochlorothiazide; **LOS** = losartan; **NR** = nonresponders; **SBP** = systolic BP; * $p < 0.01$ vs baseline.

day once daily (91%) or as a divided dose (96%) responded to therapy during the 3 months of treatment (including 52% and 68% who received lercanidipine 20 mg/day).

4.3 Treatment-Resistant Hypertension

Lercanidipine 10–30 mg/day appears effective as an add-on therapy in patients with hypertension not responding to treatment with other antihypertensive agents.[69,70] Lercanidipine 10–30 mg/day was as effective as nitrendipine 10–30 mg/day when used as add-on therapy for 12 weeks in 80 patients not responding to atenolol 50–100 mg/day, enalapril 10–20 mg/day or HCTZ/amiloride 25–50/2.5–5 mg/day.[69,70] After 4 weeks of add-on therapy, BP had normalised (DBP ≤90mm Hg) in 76% of patients receiving lercanidipine 10 mg/day and 65% of those receiving nitrendipine 10 mg/day. This increased to 89% and 91% of patients, respectively, after 12 weeks (dosages were titrated to 20 or 30 mg/day in nonresponders after 4 or 8 weeks).[69] In the second study, lercanidipine 10 mg/day caused significant reductions in seated DBP compared with placebo (8 vs 5.9mm Hg; $p = 0.025$) in 241 patients who had poorly controlled hypertension (seated DBP 95–114mm Hg) after 4 weeks of therapy with HCTZ 25 mg/day.[70]

4.4 Special Populations

4.4.1 Elderly Patients

Lercanidipine 5–30 mg/day decreased BP without affecting heart rate in elderly patients (aged >60 years) with mild-to-moderate hypertension[65-68] or isolated systolic hypertension[46] in well designed clinical trials of 8 weeks to 24 months duration. Reductions in mean BP with lercanidipine were superior to those with placebo[46,67] and similar to those with amlodipine 5–10 mg/day[66], nifedipine GITS 30–60 mg/day[68] and lacidipine 2–4 mg/day[66,68] after 24–26 weeks of therapy (table VII).

In the largest trial involving elderly patients (COHORT; n = 828), lercanidipine 10–20 mg/day reduced mean SBP/DBP by 20/10mm Hg after 4 weeks and by 30/14mm Hg after 6 months.[66] Furthermore, one study showed that the effects of lercanidipine persisted over a 24-hour period; mean

Table VII. Efficacy of lercanidipine (LER) in elderly patients (pts) [aged >60 years] with either mild-to-moderate essential hypertension (diastolic blood pressure [DBP] 96–115mm Hg)[65,66] or isolated systolic hypertension (DBP >160mm Hg and systolic blood pressure [SBP] <95mm Hg).[46] Primary endpoints were the incidence of peripheral oedema (section 5),[66] reduced blood pressure (BP) at 4 weeks[46,67] or not defined[65,68]

Reference	Age (mean) [y]	Duration of therapy	No. of pts evaluated	Starting dosage[a] (titrated dosage in NR pts[b]) [mg]	Mean SBP/DBP (mm Hg)			Normalised BP at endpoint[c] (% patients)
					baseline	4 wks	endpoint	
Noncomparative study								
Roma et al.[65]	60–90 (68)	6mo	309	LER[d]	163/95		137/81	78
Comparative studies (r, db, mc)								
Barbagallo and Barbagallo Sangiorgi[46]	>60 (67)	8 wks	37	LER 10 (20)	173/87	147**††/83**††	140**††/81**††	64††
			33	PL	172/87	166/87	163**/87**	0
Cherubini et al.[68]	>65 (73)	24 wks	84	LER 5 (10)	167/98	150/85[e]	140*/80*	96[g]
			93	LAC 2 (4)	168/98	152/84[e]	142*/81*	87‡[g]
			84	NIF GITS 30 (60)	167/97	151/84[e]	138*/79*	100[g]
Leonetti et al.[66]	≥60 (70)	6-24mo	420	LER 10 (20)	170/97	150/87[g]	140*/83*[f]	51[fg]
			200	AML 5 (10)	171/97	148/86[g]	141*/83*[f]	56[fg]
			208	LAC 2 (4)	170/97	152/87[g]	141*/8**[f]	54[fg]
Ninci et al.[67]	60–85 (68)	16 wks	88	LER 10 (30)	172/102	158*†/92*†[g]		
			45	PL	169/102	164/97[g]		

a Administration was once daily.

b Dosage titrated after 2w[68] 4w[46,66] or 2mo[65] if DBP not <90mm Hg[66] or SBP not reduced by 20 mm Hg[46] (conditions for NR not reported in third study).[65]

c DBP < 90mm Hg and/or SBP <140mm Hg.

d Abstract only. Dosage not given.

e Values are 2w after beginning therapy and are estimated from a graph.

f Values obtained after 6mo of therapy.

g Values estimated from graph.

AML = amlodipine; **db** = double blind; **LAC** = lacidipine; **mc** = multicentre; **NIF GITS** = nifedipine gastrointestinal therapeutic system; **NR** = nonresponders; **PL** = placebo; **r** = randomised; * $p < 0.01$, ** $p < 0.001$ vs baseline; † $p < 0.01$, †† $p < 0.001$ vs PL; ‡ $p < 0.001$ vs comparators.

DBP was reduced by 10.3mm Hg at 24 hours after administration of lercanidipine 10 mg/day (trough BP) compared with a peak reduction (4–5 hours post dose) of 13.3mm Hg (table VII).[67]

Lercanidipine therapy was also effective in two noncomparative studies (available as abstracts), each involving ≈300 elderly patients with mild-to-moderate hypertension.[64,65] After 2[64] or 6[65] months' treatment with lercanidipine (10 mg/day[64] or dosage not reported[65]), mean SBP and DBP were reduced from baseline by 26–28 and 13–14mm Hg ($p< 0.001$ vs baseline;[65] specific baseline and endpoint BP values not reported[64]).

In the larger study (COHORT), the number of patients with normalised BP after 6 months of lercanidipine therapy (51%; includes patients remaining on 10 mg/day and those titrated to 20 mg/day) was similar to that obtained following treatment with amlodipine 5–10 mg/day (56%) or lacidipine 2–4 mg/day (54%).[66] In contrast, larger numbers of lercanidipine recipients (receiving 5–30 mg/day) were normalised in smaller studies (64–96%; table VII), and lercanidipine titration to 20 mg/day improved the normalisation rate from 50% at week 4 to 64% at week 8 in one study.[46]

4.4.2 Other Populations

Lercanidipine effectively reduced BP in patients with type 2 diabetes and mild-to-moderate essential hypertension in a small, randomised, double-blind trial of 8 weeks duration[36] but appeared less effective in this group of patients in the ELYPSE study.[48] Mean SBP and DBP were reduced after 4 weeks in patients receiving lercanidipine 10 mg/day ($n = 19$) and in those receiving lercanidipine 20 mg/day ($n = 19$; both $p < 0.01$ vs baseline). Dosages in each group were increased by 10mg in nonresponders at week 4, with further reductions in BP occurring after 8 weeks in both treatment groups (both $p < 0.001$ vs baseline).[36] No significant differences in BP were observed between patients receiving lercanidipine 10 or 20 mg/day and those receiving 20 or 30 mg/day and BP had normalised in a similar number of patients in each group at week 4 (55% vs 50%).[36] In contrast, 16.4% of the subgroup of patients with type 2 diabetes ($n = 1269$) had adequate BP control (<130/85mm Hg) after 3 months of lercanidipine 10 mg/day in a second study (ELYPSE).[48]

Additionally, one observational study (available as an abstract) reported that lercanidipine 10 mg/day reduced BP in postmenopausal women with mild-to-moderate essential hypertension ($n = 193$; mean age 53.9 years).[73] After 6 months of lercanidipine monotherapy, mean SBP and DBP were reduced from baseline by 21.9mm Hg and 17.6mm Hg (both $p < 0.0001$) and 49% of patients had normalised BP levels (<140/90mm Hg).[73]

5. Tolerability

Lercanidipine was well tolerated in clinical trials with most treatment-emergent adverse events related to vasodilation. In the two largest studies, which involved 9059 (ELYPSE)[48] and 7046[63] patients with mild-to-moderate hypertension, adverse events were observed in 1.6 and 6.5% of patients who received lercanidipine 10 or 20 mg/day. Headache (0.2% and 2.9%), ankle oedema (0.4% and 1.2%) and flushing (1.0% and 1.1%) were the most commonly reported events. In the largest study, the majority of events were observed at the 1-month visit, and 0.9% of patients withdrew because of poor tolerability (types of event not reported).[48]

In a pooled analysis of data from 20 clinical trials involving almost 1800 patients with hypertension, 11.8% of lercanidipine recipients (10 or 20 mg once daily; $n = 1317$) reported adverse events compared with 7.0% of those receiving placebo ($n = 227$).[74] The percentage of patients who withdrew from treatment, independent of the reason, was similar in both groups (12.8% and 8.4%). Patients receiving lercanidipine or placebo withdrew for the following reasons: adverse effects (5% and 3%; not clinically significant), lack of efficacy (1% and 1%) and undefined or personal reasons (6% and 4%). The most commonly reported adverse events for lercanidipine (including patients receiving a 10 or 20mg starting dose and 20mg titrated dose) versus placebo recipients were headache (1.7–2.3% vs 1.3%), flushing (0.9–6.1% vs 0.4%), vertigo (0.2–0.6% vs 0.4%),

palpitations (0.6–8.9 vs 0.4%) and ankle oedema (0.9–6.1% vs 1.3%).

Lercanidipine was also well tolerated in elderly patients (aged >60 years) during both short-term (8–24 weeks)[46,67,68] and longer-term treatment (>6 months).[65,66] Adverse events were reported by <3–19.4% of patients receiving lercanidipine 10 or 20 mg/day. Peripheral oedema was the most common event recorded (2.3–9.3%), although increased liver enzymes, flushing and headache were also reported in several studies. A small number of elderly lercanidipine recipients withdrew from clinical trials because of adverse events that included due to distal oedema (2 of 309),[65] dyspepsia (2 of 96),[68] headache, gastric discomfort and/or fever (4 of 88)[67] and epigastric pain (1 of 37).[46] Where reported, the incidence of adverse events was similar in elderly patients receiving lercanidipine 10 mg/day and those receiving 20 mg/day (7.1–11.2% vs 8.3–11.1%)[21,46,67]

Recommended dosages (10 or 20 mg/day) of lercanidipine generally did not significantly alter heart rate in patients with essential hypertension,[14,16-24] except for a small but significant reduction in heart rate observed after 1 and 3 months of treatment with lercanidipine 10 mg/day in the ELYPSE study ($p < 0.01$ vs baseline; the clinical relevance of this reduction was not reported).[48] Furthermore, consistent with findings detailed in section 2.4, lercanidipine was well tolerated with regard to ECG parameters in clinical trials.[14,17-22,45-47,49]

5.1 Comparisons with Other Antihypertensive Agents

Well designed clinical trials have shown that lercanidipine 10 or 20 mg/day has a similar tolerability profile to captopril 50–100 mg/day,[18] atenolol 50–100 mg/day[21] and losartan 50–100 mg/day.[20] Headache and oedema were the most common adverse events reported and the incidence was similar between treatment groups.

When compared with the calcium channel antagonists nitrendipine (10 or 20 mg/day),[69] nifedipine SR (20–40mg twice daily)[45] and nifedipine GITS (30–60mg once daily),[47,68] lercanidipine 5–20mg once daily for 8,[47] 12,[69] 16[45] or 24 weeks[68] was associated with a lower overall incidence of adverse events (figure 2). Fewer withdrawals were also reported for lercanidipine recipients although the difference was not statistically significant.[45]

In the large, long-term COHORT study (6–24 months) involving 828 elderly (aged >60 years) patients with mild-to-moderate hypertension, 26% of lercanidipine recipients (10–20 mg/day) reported an adverse event compared with 28% and 22% of those receiving amlodipine (5–10mg/day) and lacidipine (2–4 mg/day).[66] Peripheral oedema (the primary endpoint) was the most common adverse event reported in all three treatment groups, the incidence rate in lercanidipine recipients being approximately half that of amlodipine recipients (9.3% vs 19%; $p < 0.001$). This same study reported that the incidence of oedema in patients receiving lacidipine was 4.3% (odds ratio [OR] = 0.44 [95% CI, 0.21–0.93]). There was no significant difference in the number of patients receiving lacidipine or lercanidipine who were withdrawn from study treatment because of peripheral oedema (1.4% vs 2.4%; OR = 0.67 [95%CI, 0.18–2.5]).[66]

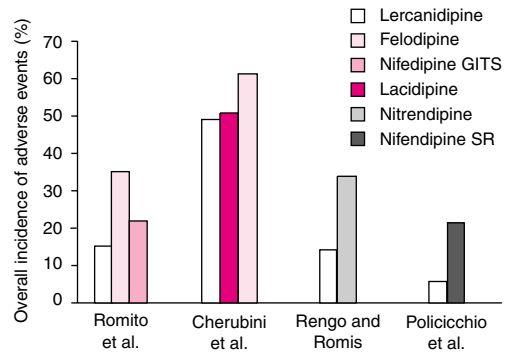

Fig. 2. Overall total incidence of adverse events during therapy for 8–24 weeks with lercanidipine 5–30 mg/day compared with other calcium channel antagonists (felodipine 10–20 mg/day, nifedipine gastrointestinal therapeutic system [GITS] 30–60 mg/day, lacidipine 2–4 mg/day, nitrendipine 10–30 mg/day and nifendipine slow release [SR] 20–40 mg/day) in patients aged 54–58[45,47,69] or >65[68] years with mild-to-moderate[45,47,68] or severe[69] hypertension. All studies (Romito et al.,[47] Cherubini et al.,[68] Rengo and Romis[69] and Policicchio et al.[45]) were randomised, double-blind and parallel-group in design.

In contrast, the incidence of oedema in the 24-week Elderly and Lercanidipine (ELLE) study, involving 324 elderly patients (aged >65 years) with mild-to-moderate hypertension, was 2.8% and 6.4% ($p < 0.10$) in those treated with lercanidipine 5–10 mg/day or lacidipine 2–4 mg/day although the percentage of patients withdrawing from treatment because of oedema was similar in both groups (1.9% vs 1.9%) and less than that reported in nifedipine recipients (7.3%).[68] It should be noted that in this study, patients received dosages of lercanidipine (5–10 mg/day) lower than those currently recommended (section 6) whereas patients in the lacidipine treatment arm received the approved dosage of study drug (2–4 mg/day; table VII).

Furthermore, a noncomparative, multicentre study in 115 patients who had reported adverse vasodilation as an adverse event while taking amlodipine, nifedipine GITS, felodipine or nitrendipine showed that the prevalence of this adverse event was significantly reduced after patients switched to lercanidipine 10–20 mg/day for 4 weeks before being rechallenged with the original drug for 4 weeks.[75] Overall, the incidence of oedema was reduced by 46%, flushing by 51% and headache and rash both by 53% (all $p < 0.001$).

6. Dosage and Administration

Oral lercanidipine is available in most of Europe (including the UK), Asia, Australasia and South America for the treatment of hypertension. UK prescribing information indicates that lercanidipine therapy should be used for the treatment of mild-to-moderate hypertension, with the dosage initiated at 10mg once daily, given at least 15 minutes before meals (to enhance absorption, section 3.1).[58] The dosage can be increased to 20 mg/day in patients who do not respond satisfactorily after a minimum of 2 weeks (as maximal antihypertensive effect may not be apparent until after this time).[58]

Dosage adjustments are not required when initiating treatment in the elderly or in patients with mild-to-moderate renal or hepatic dysfunction, although treatment should be initiated and titrated with caution.[58] Lercanidipine is not recommended for use in patients with severe hepatic or renal dysfunction (creatinine clearance <10 mL/min), nor in patients aged <18 years.

Lercanidipine is contraindicated during pregnancy and lactation, in women of child-bearing potential unless effective contraception is used, in patients with left ventricular outflow tract obstruction, untreated congestive heart failure, unstable angina pectoris or within one month of a myocardial infarction.[58] The manufacturer also recommends that special care should also be taken when administering lercanidipine to patients with sick sinus syndrome if a pacemaker is not *in situ*.[58]

Lercanidipine should not be coadministered with inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole and erythromycin), or with cyclosporin or grapefruit juice. Furthermore, caution should be exercised when administering lercanidipine with inducers (e.g. phenytoin, carbamazepine and rifampicin) or other substrates (midazolam, metoprolol, propranolol and amiodarone) of CYP3A4. [58] In addition, dosage adjustments may be required when β–adrenoceptor antagonists are administered concomitantly.[58]

Lercanidipine can be safely coadministered with warfarin, simvastatin, β-methyldigoxin and low dosages of cimetidine (≤800 mg/day); however, patients receiving concomitant digoxin should be monitored for digoxin toxicity.[58]

7. Place of Lercanidipine in the Management of Hypertension

Hypertension is a major risk factor for heart disease and stroke,[1] and with the prevalence of hypertension reaching 20% in Western populations,[4,44] the disease currently places an enormous financial burden on healthcare systems. For this reason, effective management of hypertension is a primary healthcare objective in most countries, with intervention involving both lifestyle modifications and pharmacological therapy.[76]

Guidelines for the management of hypertension vary slightly; however, those published recently by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pres-

sure (Seventh Report [JNC-VII], May 2003)[77] and the European Society of Hypertension (ESH; June 2003)[53] recommend reducing BP to below 140/90mm Hg (if tolerated) and to less than 130/80mm Hg in high-risk populations such as those with diabetes or renal disease.

The JNC-VII guidelines suggest that therapy for hypertension should be initiated with diuretics, either alone or in combination with one of the other drug classes (ACE inhibitors, β-adrenoreceptor antagonists, angiotensin II-receptor blockers, calcium channel antagonists).[77] However, the JNC-VII also recommends that calcium channel antagonists can be used as first-line therapy in patients with isolated systolic hypertension and in those with coexisting angina pectoris.[78] In contrast, ESH guidelines suggest that all classes of drug can be used for both the initiation and maintenance of antihypertensive therapy.[53]

Lercanidipine is a third generation dihydropyridine calcium channel antagonist that has demonstrated antihypertensive efficacy in patients with mild-to-moderate hypertension. Clinical studies indicate that lercanidipine 10–20 mg/day is as effective at reducing BP as nifedipine SR 20–40mg twice daily, amlodipine 10mg once daily, felodipine 10–20 mg/day, verapamil 240mg once daily, losartan 50–100 mg/day and nifedipine GITS 30–60mg once daily in patients with mild-to-moderate hypertension during short-term therapy (section 4.1.3). Mean peak reductions in 24-hour BP, as measured using ABPM monitoring, were also similar to those with other calcium channel antagonists. Furthermore, lercanidpine 10–20 mg/day significantly reduced BP in two large, noncomparative trials involving a total of >16 000 patients with grade 1, 2 or 3 hypertension (section 4.1.1).

Guidelines agree that most patients with hypertension require two or more antihypertensive agents to achieve goal BP levels. The use of agents with acceptable adverse event profiles, particularly when used in combination therapy, is therefore crucial to the success of an antihypertensive therapy regime. Limited studies have suggested that the combination of a calcium channel blocker with an ACE-inhibitor results in an additive antihypertensive effect with an improved adverse event profile.[79] Furthermore, lercanidipine effectively reduced BP when used as add-on therapy in patients who were not responding sufficiently to monotherapy with atenolol (β-blocker), HCTZ (diuretic) or enalapril (ACE inhibitor) [section 4.3] and no adverse events due to combination therapy were reported.

Lercanidipine was well tolerated during monotherapy in patients with mild-to-moderate hypertension. Adverse events were generally associated with vasodilation and included headache, dizziness, flushing and oedema. Importantly, lercanidipine 10–20 mg/day was associated with a lower incidence of oedema than amlodipine 5–10 mg/day or nifedipine GITS 30 mg/day (section 5.1), and treatment withdrawals due to oedema were similar in patients treated with lercanidipine 10–20 mg/day or lacidipine 2–4 mg/day.

Lercanidipine therapy was also effective in elderly patients (>60 years) with either mild-to-moderate hypertension or isolated systolic hypertension (section 4.4.1). Reductions in BP with lercanidipine 5–30 mg/day were similar to those with amlodipine 5–10 mg/day, nifedipine GITS 30–60 mg/day and lacidipine 2–4 mg/day after 24–26 weeks of therapy. In addition, the frequency of adverse events reported in each treatment group was similar (section 5.1). As assessed in a small number of studies, lercanidipine may also reduce BP in patients with severe hypertension (section 4.2)[22] and those with mild-to-moderate hypertension and type 2 diabetes (section 4.4.2).[36,48] Further investigation is required to substantiate these findings.

The JNC-VII and ESH guidelines, as well as those provided by the World Health Organization - International Society of Hypertension (WHO-ISH)[80] and the British Hypertension Society (BSH),[76] agree that the primary goal of hypertension is to reduce morbidity and mortality by lowering BP and modifying other cardiovascular risk factors. Research suggests that calcium channel antagonists may effectively reduce cardiovascular mortality and morbidity,[56,78,81,82] but specific clinical studies with lercanidipine have presently not

been undertaken. However, data suggests that lercanidipine can reduce left ventricular hypertrophy (section 2.4) and may improve the glucose profile (section 2.6) in patients with mild-to-moderate hypertension and diabetes. It would be therefore be of clinical interest to substantiate these findings and to assess the direct effect of lercanidipine therapy on the incidence of cardiovascular morbidity/mortality.

Current prescribing information suggests that lercanidipine therapy should be initiated at a dosage of 10 mg/day and titrated after 2 weeks to a higher dose (20 mg/day) gradually in patients who are not responding to therapy (section 6).[58] Recent clinical findings have demonstrated that the number of patients responding to therapy or with normalised BP (<140/90mm Hg) can be increased when dosage is increased to 20 mg/day in nonresponder patients (section 4). As such, a dosage of 20 mg/day may be necessary in some patients with mild-to-moderate or severe hypertension for effective BP control (section 4).

In conclusion, lercanidipine is an effective and well tolerated antihypertensive agent in patients with mild-to-moderate hypertension after once-daily administration. Furthermore, in limited, studies the drug has demonstrated efficacy in patients with severe or resistant hypertension (as add-on therapy), in the elderly and in patients with type 2 diabetes. Importantly, lercanidipine appears to be as effective and at least as well tolerated as many other calcium channel antagonists, but with a decreased incidence of peripheral oedema. Limited studies also suggest that this drug is an effective component in combination therapy. Lercanidipine is therefore an appropriate option for the treatment of patients with mild-to-moderate essential hypertension.

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