AUSTRALIAN PRODUCT INFORMATION

ZAN-EXTRA®

Lercanidipine hydrochloride and Enalapril maleate film-coated tablets

1 NAME OF THE MEDICINE

Lercanidipine hydrochloride and Enalapril maleate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZAN-EXTRA film-coated tablets are immediate release film-coated tablets for oral use.

Each ZAN-EXTRA 10/10 film-coated tablets contains 10 mg of lercanidipine hydrochloride and enalapril maleate 10 mg as the active ingredients.

Each ZAN-EXTRA 10/20 film-coated tablets contains 10 mg of lercanidipine hydrochloride and enalapril maleate 20 mg as the active ingredients.

Excipients with known effect:

ZAN-EXTRA 10/10 - sugars as lactose

ZAN-EXTRA 10/20 - lactose

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

ZAN-EXTRA 10/10 tablets are white, circular, biconvex, film-coated tablets.

ZAN-EXTRA 10/20 tablets are yellow, circular, biconvex, film-coated tablets.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of hypertension.

Treatment should not be initiated with these fixed dose combinations (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dosage for ZAN-EXTRA tablets is one tablet once daily taken orally at least 15 minutes before meals. ZAN-EXTRA should not be taken with grapefruit juice (see Section 4.3 CONTRAINDICATIONS and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

The 10 mg/10 mg strength tablets may be administered to patients whose blood pressure is not adequately controlled on lercanidipine 10 mg alone.

The 10 mg/20 mg strength tablets may be administered to patients whose blood pressure is not adequately controlled on enalapril 20 mg alone.

The administration of the 10 mg/20 mg tablets to patients whose blood pressure was not controlled by 10 mg/10 mg has proved to be well tolerated. No randomised study has compared the efficacy of the two strengths or 10 mg/10 mg tablets versus enalapril 10 mg alone.

In each case, when clinically appropriate, a direct change from monotherapy to the fixed combination may be considered.

Replacement therapy: For convenience, patients receiving lercanidipine and enalapril from separate tablets may instead wish to receive the combination tablets.

4.3 CONTRAINDICATIONS

- Hypersensitivity to lercanidipine or enalapril, to any dihydropyridine calcium antagonist or ACE inhibitor, or to any of the excipients.
- Pregnancy (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in Pregnancy).
- Lactation (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in Lactation).
- Women of child-bearing potential unless effective contraception is used.
- Severe renal impairment (GFR < 30 mL/min), including patients undergoing dialysis.
- Severe hepatic impairment.
- Co-administration with:
    - Ciclosporin (see Section 4.4 Special WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**)**
    - Strong CYP3A4 inhibitors
    - Grapefruit or grapefruit juice
    - With aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min)
    - Sacubitril/valsartan. Enalapril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan
- History of angioedema, whether hereditary or idiopathic, or associated with previous ACE inhibitor therapy.
- Left ventricular outflow track obstruction.
- Untreated congestive cardiac failure.
- Unstable angina pectoris or recent (within 1 month) myocardial infarction.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including enalapril maleate. This may occur at any time during treatment. In such cases, ZAN-EXTRA should be promptly discontinued and the patient carefully observed until the swelling disappears. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient. Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous adrenaline (epinephrine) solution 1:1000 (0.3 mL to 0.5 mL) and/or measures to ensure a patent airway should be promptly administered** [see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

The onset of angioedema associated with use of ACE inhibitors may be delayed for weeks or months. Patients may have multiple episodes of angioedema with long symptom-free intervals. Angioedema may occur with or without urticaria.

Black patients receiving ACE inhibitors have been reported to have higher incidence of angioedema compared to non-blacks.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see Section 4.3 CONTRAINDICATIONS).Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of enalapril. Treatment with enalapril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see Section 4.3 CONTRAINDICATIONS and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus and temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Caution should be used when starting racecadotril mTOR inhibitors and vildagliptin in a patient already taking an ACE inhibitor.

Symptomatic hypotension

Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving enalapril, symptomatic hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed and may be associated with oliguria and/or progressive azotaemia, and rarely with acute renal failure and/or death. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatremia or functional renal impairment. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision and the patient should be followed closely whenever the dose of enalapril and/or diuretic is adjusted. Similar considerations may apply to patients with ischaemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with enalapril. This effect is anticipated and usually is not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction in the dose and/or discontinuation of the diuretic and/or enalapril may be necessary.

Neutropenia/Agranulocytosis

Another angiotensin converting enzyme inhibitor has been shown to cause agranulocytosis and bone marrow depression (including leucopenia/neutropenia). Enalapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol, procainamide or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. International marketing experience has revealed cases of neutropenia or agranulocytosis, in which a causal relationship to enalapril cannot be excluded.

It is recommended that periodic haematologic monitoring be considered in patients with diseases known to affect bone marrow function (e.g. renal dysfunction, collagen vascular disease etc.) and/or who are taking concomitant therapy known to be associated with bone marrow depression.

Sick Sinus Syndrome

Special care should be exercised when lercanidipine is used in patients with sick sinus syndrome (if a pacemaker is not in situ).

Lercanidipine does not interfere with normal cardiac excitation and conduction when used at therapeutic dosages in patients with mild to moderate hypertension as clearly demonstrated below.

Two invasive cardiac catheterisation studies were performed:

Lercanidipine: a novel lipophilic dihydropyridine calcium antagonist with long duration of action and high vascular selectivity. Studies were performed with single oral doses of lercanidipine. No evidence of reduced cardiac inotropism were found in the studies and no changes in ECG parameters, including PR and RR intervals were observed. In addition, an open invasive ECG study found no negative effect on the sinus node and A-V conduction functional parameters 1.5 to 2 h after a single oral dose of lercanidipine 20 mg.

A randomised, double-blind study in patients with mild to moderate hypertension was conducted to compare the effects of prolonged (2 weeks) administration of lercanidipine 20 mg once daily with those of sustained-release (SR) verapamil 240 mg once daily on cardiac excitation and conduction. The results demonstrated that lercanidipine does not interfere with normal cardiac excitation and conduction since it has no significant effect on QRS duration, or PR, QT and QTc intervals. In addition, lercanidipine had no effects on the types of cardiac arrhythmias present in these patients. The effects of lercanidipine were generally similar to those of verapamil SR, although verapamil trended to prolong the PR interval.

Ischaemic Heart Disease

It has been suggested that some short-acting dihydropyridines may be associated with increased cardiovascular risk in patients with ischaemic heart disease. Although lercanidipine is long-acting, caution is required in such patients.

Left Ventricular Dysfunction

Although haemodynamic controlled studies revealed no impairment of ventricular function, care is required in patients with left ventricular outflow obstruction (aortic stenosis) when treated with calcium channel blockers.

ACE inhibitors should be given with caution to patients with left ventricular valvular and outflow obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Congestive Heart Failure

In general, calcium channel blockers should be used with caution in patients with heart failure. Although animal data and acute haemodynamic evaluation in patients with preserved left ventricular function have not demonstrated that lercanidipine exerts a direct negative inotropic effect, safety in patients with congestive heart failure has not been established. Therefore, as for other calcium channel blockers, lercanidipine should be used with caution in such patients, especially if untreated.

Unstable Angina Pectoris or Within One Month of a Myocardial Infarction

Rarely, patients have developed documented increased frequency, duration and/or severity of angina on starting calcium channel blocker therapy or at the time of dosage increase (particularly those with severe obstructive coronary artery disease). The mechanism of this effect has not been elucidated, however the possibility of an exacerbation of angina and/or cardiac ischaemia exists. It is therefore suggested that the use of calcium channel blockers is not advisable in patients with unstable angina pectoris or recent myocardial infarction [see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS**)**].

Combination use of Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Antagonists and Anti-inflammatory Drugs and Thiazide Diuretics

The use of an ACE inhibitor or angiotensin receptor antagonist and an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of renal function, particularly at the institution of the treatment. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Dual Blockade of the Renin-angiotensin-aldosterone System (RAAS)

There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 5.1 PHARMACODYNAMIC PROPERTIES).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Anaphylactoid Reactions During Hymenoptera Desensitisation or LDL-Apheresis

Rarely, patients receiving ACE inhibitors during desensitisation with hymenoptera venom (for example, from bees, ants or wasps), or during low density lipoprotein (LDL)-apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each desensitisation or apheresis.

Haemodialysis Patients

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (polyacrylonitrile membranes e.g. AN 69) and treated concomitantly with an ACE inhibitor. These patients should be given a different type of dialysis membrane or a different class of antihypertensive agent.

Peritoneal Dialysis

Lercanidipine has been associated with the development of cloudy peritoneal effluent in patients on peritoneal dialysis. The turbidity is due to an increased triglyceride concentration in the peritoneal effluent. Whilst the mechanism is unknown, the turbidity tends to resolve soon after withdrawal of lercanidipine. This is an important association to recognise as cloudy peritoneal effluent can be mistaken for infective peritonitis with consequential unnecessary hospitalisation and empiric antibiotic administration.

Hypoglycaemia

Diabetic patients treated with oral antidiabetic agents or insulin and who are starting an ACE inhibitor should be told to closely monitor for hypoglycaemia, especially during the first month of treatment with this combination (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Cough

A persistent, non-productive, ticklish cough has been reported in some patients undergoing treatment with enalapril and other ACE inhibiting drugs. The cough is often worse when lying down. The cough is commoner in women (who account for about two thirds of reported cases). The patients who cough may have increased bronchial reactivity compared to those who do not cough. It may disappear in some patients with continued use, or diminish or disappear if the dose of the drug is reduced.

In those in whom cough persists, the drug should be discontinued. The cough usually returns on rechallenge. No residual effects have been reported.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia

Elevated serum potassium (greater than 5.7 mmol/L was observed in approximately one percent of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalaemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Risk factors for the development of hyperkalaemia may include renal insufficiency, diabetes mellitus and the concomitant use of potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril.

The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal, arrhythmias.

If concomitant use of enalapril and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium and renal function.

Serum Lithium

The combination of lithium and enalapril is not recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Ethnic Differences

As with other ACE inhibitors, enalapril is apparently less effective in lowering blood pressure in black patients than in non-blacks, possibly because plasma renin levels are often lower in the black hypertensive population.

Alcohol

Alcohol should be avoided because it may potentiate the effect of vasodilating antihypertensive drugs (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Lactose

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose/galactose malabsorption should not take this medicine.

Use in Hepatic Impairment

ZAN-EXTRA is contraindicated in patients with severe hepatic impairment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.3 CONTRAINDICATIONS).

The antihypertensive effect of lercanidipine may be enhanced in patients with hepatic impairment.

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Use in Renal Impairment

ZAN-EXTRA tablets are contraindicated in patients with severe renal impairment (GFR <30 mL/min) (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.3 CONTRAINDICATIONS).

Caution should be exercised with enalapril when initiating treatment in patients with mild to moderate renal impairment. Routine monitoring of serum potassium and creatinine are part of normal medical practice for these patients.

Renal failure has been reported in association with enalapril, mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognised promptly and treated appropriately, renal failure, when associated with enalapril therapy, is usually reversible.

Some hypertensive patients, with no apparent pre-existing renal disease have developed increases in blood urea and serum creatinine, when enalapril has been given concurrently with a diuretic. Dose reduction of enalapril and/or discontinuation of the diuretic, may be required. This situation should raise the possibility of underlying renal artery stenosis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Renovascular Hypertension).

Evaluation of the hypertensive patient should always include assessment of renal function (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Kidney Transplantation

There is no experience regarding the administration of lercanidipine or enalapril in patients with recent kidney transplantation. Treatment with ZAN-EXTRA is therefore not recommended.

Renovascular Hypertension

There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery due to a single functioning kidney are treated with ACE inhibitors. Loss of renal function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under close medical supervision with low doses, careful titration and monitoring of renal function.

Use in the Elderly

The dose for elderly patients should be in line with their renal function. ZAN-EXTRA is contraindicated in severe renal impairment (GFR < 30 mL/min) or in patients on haemodialysis (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in Renal Impairment). Special care should be exercised when treatment is commenced in patients with mild to moderate impairment of kidney function.

When concomitantly administered with midazolam to elderly volunteers, lercanidipine absorption was increased and the rate of absorption was decreased. Midazolam concentrations were not modified.

Paediatric Use

Since there is no clinical experience in patients under the age of 18 years, use in children is not recommended.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The antihypertensive effect of ZAN-EXTRA could be potentiated by other antihypertensive drugs such as diuretics, beta-blockers, alpha-blockers and other medicines.

The following interactions have been observed with one or the other components of the combination.

Lercanidipine

Contraindications of concomitant use

Inhibitors of CYP3A4

Since the main metabolic pathway of lercanidipine involves the enzyme CYP3A4, drugs that inhibit this enzyme have the potential to alter the plasma concentration of the compound.

An interaction study with a strong CYP3A4 inhibitor, ketoconazole, has shown a considerable increase in plasma levels of lercanidipine (a 15-fold increase of the AUC and an 8-fold increase of the C_{max} for the eutomer S-lercanidipine).

Therefore, inhibitors of CYP3A4 (such as ketoconazole, itraconazole, erythromycin, ritonavir, troleandomycin, clarithromycin) may increase the plasma concentration of lercanidipine, and such combinations should be avoided.

Ciclosporin

Co-administration of lercanidipine with ciclosporin resulted in a 3-fold increase in the plasma levels of lercanidipine and a 21% increase in the bioavailability of ciclosporin. However, when ciclosporin was administered 3 hours after lercanidipine, no increase in plasma levels was observed for lercanidipine, while the bioavailability of ciclosporin increased by 27%. Therefore, ciclosporin and lercanidipine should not be administered together.

Grapefruit or grapefruit juice

The metabolism of dihydropyridines can be inhibited by grapefruit juice, leading to increased plasma concentration and hypotensive effect. Lercanidipine should not be taken with grapefruit or grapefruit juice (see Section 4.3 CONTRAINDICATIONS).

Concomitant use not recommended

Inducers of CYP3A4

When co-administered with CYP3A4 inducers, such as anticonvulsants (e.g. phenytoin, phenobarbital (phenobarbitone), carbamazepine) and rifampicin, the antihypertensive effect of lercanidipine may be reduced and, therefore, blood pressure should be monitored when the co-administration is foreseen.

Alcohol

Alcohol should be avoided while taking lercanidipine since it may potentiate the effect of vasodilating antihypertensive drugs.

Precaution including dose adjustment

CYP3A4 and CYP2D6 Substrates

The potential for *in vivo* inhibition of CYP3A4 by lercanidipine is negligible, as confirmed by an interaction study with midazolam in healthy volunteers. After repeated co-administration with lercanidipine, midazolam (a probe for CYP3A4 activity) was found to be essentially bioequivalent to the drug administered alone. However, unless specific data are available, caution should also be exercised when lercanidipine is co-prescribed with other substrates of CYP3A4 which have a narrow therapeutic index, such as ciclosporin and class III antiarrhythmic drugs (e.g. amiodarone, sotalol and quinidine).

Moreover, interaction studies in humans have shown that lercanidipine did not modify the plasma levels of metoprolol (a typical substrate of CYP2D6) but did reduce the bioavailability of lercanidipine by 50%. The effect may be due to the reduction in hepatic blood flow caused by β-blockers and may occur with other drugs of this class. Therefore, at therapeutic doses, it is unlikely that lercanidipine will inhibit the biotransformation of drugs metabolised by CYP2D6 but dose adjustment may be required. It is anticipated that a similar effect may occur with propranolol.

These findings confirm that the inhibition of cytochrome P450 isoenzymes observed *in vitro* with lercanidipine is devoid of any clinical significance. *In vitro* experiments with human liver microsomes demonstrated that lercanidipine inhibits CYP3A4 and CYP2D6 (IC_{50} of 2.6 µm and 0.8 µm, respectively). The IC_{50} concentrations for CYP3A4 and CYP2D6 are 160 and 40-fold higher, respectively, than those reached at peak in the plasma after a 20 mg dose.

Cardiac Glycosides

Co-administration of 20 mg lercanidipine in patients chronically treated with beta-methyldigoxin (a pro-drug of digoxin) showed no evidence of a pharmacokinetic interaction. Increases in digoxin C_{max} have been observed, while AUC and renal clearance were not significantly modified. However, patients on concomitant digoxin treatment should be closely monitored for signs of digoxin toxicity.

Concomitant use with other drugs

Fluoxetine

An interaction study with fluoxetine (an inhibitor of CYP2D6 and CYP3A4), conducted in volunteers of an age of 65 ± 7 years (mean ± s.d.) has shown no clinically relevant modification of the pharmacokinetics of lercanidipine.

Cimetidine

Concomitant administration of cimetidine 400 mg BD does not cause significant changes in the plasma levels of lercanidipine: AUC and C_{max} were increased by a mean of 11%. However, at higher doses caution is required since the bioavailability and the hypotensive effect of lercanidipine may be increased.

Simvastatin

Co-administration of a 20 mg dose of lercanidipine with 40 mg simvastatin resulted in no increase in the bioavailability of lercanidipine, however a 56% increase was observed for simvastatin and a 28% increase for its active metabolite β-hydroxyacid. It is unlikely that these changes are clinically relevant. However, it is recommended that when required lercanidipine be administered in the morning and simvastatin in the evening.

Food

For the effect of food on bioavailability see Section 5.2 PHARMACOKINETIC PROPERTIES.

For the effect of alcohol and grapefruit juice see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

Warfarin

Co-administration of lercanidipine 20 mg to fasting, healthy volunteers did not alter the pharmacokinetics of warfarin.

Diuretics and ACE Inhibitors

Lercanidipine has been safely administered with diuretics and ACE inhibitors.

Other Medications Affecting Blood Pressure

As for all antihypertensive medications, an increased hypotensive effect may be observed when lercanidipine is administered with other medicines affecting blood pressure, such as alpha-blockers for the treatment of urinary symptoms, tricyclic antidepressants and neuroleptics.

A reduction of the hypotensive effect may be observed with concomitant use of corticosteroids.

Enalapril

Potassium-sparing Diuretics, Potassium Supplements or Potassium-containing Salt Substitutes

ACE inhibitors attenuate diuretic induced potassium loss. Potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium in some patients treated with enalapril. Care should be taken when enalapril is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Diuretics (thiazide or loop diuretics)

Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure with enalapril treatment. The possibility of hypotensive effects with enalapril can be minimised by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril or by initiating therapy with a low dose of enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least one hour after the initial dose (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Dual blockade of renin-angiotensin-aldosterone system (RAAS)

The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g. diuretics).

Combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single renin-angiotensin-aldosterone system-acting agent.

Other Antihypertensive Agents

Concomitant use of these agents may increase the hypotensive effects of enalapril. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure. However, enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Ciclosporin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

Lithium

As with other drugs which eliminate sodium, lithium clearance may be reduced. Concomitant use of thiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Therefore, the serum lithium levels should be monitored carefully if lithium salts are to be administered (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Tricyclic Antidepressants/Antipsychotics/Anaesthetics/Narcotics

Concomitant use of certain anaesthetics, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. Therefore, the antihypertensive effect of angiotensin II receptor antagonists or ACE inhibitors may be attenuated by NSAIDs, including COX-2 inhibitors.

In some patients with compromised renal function (e.g. elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with NSAIDs including COX-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible renal failure. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function (e.g. the elderly, patients who are volume-depleted including those on diuretic therapy).

These interactions should be considered in patients taking NSAIDs including COX-2 inhibitors concomitantly with diuretics, angiotensin II receptor antagonists and ACE inhibitors. Therefore, such a combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and monitoring of renal function after initiation of concomitant therapy should occur periodically.

Antidiabetics

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose- lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored for hypoglycaemia, especially during the first month of treatment.

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including enalapril.

Medicines Increasing the Risk of Angioedema

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Coadministration of an ACE inhibitor, racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus and temsirolimus) and vildagliptin may increase the risk of angioedema (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Alcohol

Alcohol enhances the hypotensive effect of ACE inhibitors.

Aspirin, Thrombolytics and β-blockers

Enalapril can be safely administered concomitantly with aspirin (at cardiologic doses), thrombolytics and β-blockers.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Further preclinical studies have not been carried out with ZAN-EXTRA. Such data are available with the two active components.

Reproductive studies in animals using the combination have not been performed.

Lercanidipine

Administration of lercanidipine at oral doses up to 12 mg/kg/day (associated with exposures, based on AUC, about 40-80 times the expected human exposure at 10 mg/day) had no effect on male or female fertility in rats.

Enalapril

There were no adverse effects on reproductive performance in male or female rats treated with enalapril 10-90 mg/kg/day.

Use in Males

Reversible biochemical changes in the head of spermatozoa which can impair fecundation have been reported in some patients treated by channel blockers. In cases where repeated *in vitro* fertilisation is unsuccessful and where another explanation cannot be found, the possibility of calcium channel blockers as the cause should be considered.

Use in Pregnancy

Pregnancy Category: D

ZAN-EXTRA is contraindicated in pregnancy (see Section 4.3 CONTRAINDICATIONS).

There are no or limited data from the use of enalapril/lercanidipine in pregnant women.

Pregnancy should be excluded before starting treatment with ZAN-EXTRA and avoided during treatment.

If a patient intends to become pregnant whilst taking ZAN-EXTRA, treatment must be discontinued and replaced by another form of treatment.

If a patient becomes pregnant while on treatment, she must immediately inform her doctor to discuss a change in medication and further management.

Lercanidipine

There is no clinical experience with lercanidipine in pregnancy, but other dihydropyridine compounds have been found to cause irreversible malformations in animals. Therefore, lercanidipine should not be administered during pregnancy or to women of child-bearing potential unless effective contraception is used.

In animal studies, pregnant rats given lercanidipine orally at doses greater than or equal to 2.5 mg/kg/day showed signs of dystocia, an increased incidence of stillbirths and a lower neonatal survival index.

The no-effect dose for effects on parturition and neonatal survival was 0.5 mg/kg/day, associated with systemic exposure (AUC) similar to the expected human exposure when dosing started before pregnancy or 2.5

mg/kg/day (about 6 times the human AUC) when dosing started during early gestation. Lercanidipine doses of 2.5 mg/kg/day during gestation also caused a higher incidence of fetal visceral abnormalities (mono/bilateral renal pelvic and/or ureteric dilatation) and skeletal abnormalities (mainly delayed ossification) at all dose levels. The effects of lercanidipine during pregnancy have not been investigated adequately in a non-rodent species.

Enalapril

There are no adequate and well controlled studies of enalapril in pregnant women. Data, however, show that enalapril crosses the human placenta. Post-marketing experience with all ACE inhibitors suggest that exposure *in utero* may be associated with hypotension and decreased renal perfusion in the fetus. ACE inhibitors have also been associated with fetal death *in utero.*

There is a potential risk of fetal hypertension, decreased birth weight and decreased renal perfusion or anuria in the fetus from *in utero* exposure to ACE inhibitors. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Any neonate exposed to enalapril *in utero* should be observed closely for adequate urine output, blood pressure and hyperkalaemia. If required, appropriate medical measures should be initiated including administration of fluids or dialysis to remove enalaprilat from the circulatory system.

Maternal and fetal toxicity occurred in some rabbits at doses equal to or greater than 1 mg/kg/day. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day. Enalapril was not teratogenic in rabbits. There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril. Fetotoxicity shown as decreased average fetal weight, occurred in rats given 1,200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline.

Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Use in Lactation

ZAN-EXTRA is contraindicated in lactation (see Section 4.3 CONTRAINDICATIONS).

Enalapril and its active metabolite, enalaprilat, are excreted in breast milk.

Lercanidipine is highly lipophilic and is expected to be excreted in human milk. Breastfeeding patients should not take ZAN-EXTRA, or if use of the medicine is essential, breastfeeding should be discontinued.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Clinical experience with ZAN-EXTRA and its components indicates that has a minor influence on the ability to drive or use machinery. However, caution should be exercised because dizziness, asthenia, fatigue and, rarely, somnolence may occur.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse reactions observed with the fixed combination are similar to the ones occurring with one or other of the components when administered alone. The most commonly reported adverse reactions during treatment with ZAN-EXTRA were cough, dizziness and headache.

In the table below, adverse reactions reported in clinical studies with ZAN-EXTRA 10 mg/10 mg and 10 mg/20 mg and for which a reasonable causal relationship exists are listed by MedDRA system organ class and frequency: very common (>1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (<1/10,000) not known (cannot be estimated from the available data).

Blood and lymphatic system disorders	
Uncommon:	Thrombocytopenia

Rare:	Haemoglobin decreased
Immune System Disorders	
Uncommon:	Hypersensitivity*
Metabolism and nutrition disorders	
Uncommon:	Hyperkalaemia, hypertriglyceridaemia*
Psychiatric disorders	
Uncommon:	Anxiety
Nervous system disorders	
Common:	Dizziness, headache (including postural dizziness)
Uncommon:	Loss of consciousness*
Ear and labyrinth disorders	
Common:	Vertigo
Rare:	Tinnitus
Cardiac disorders	
Uncommon:	Tachycardia, palpitations
Vascular disorders	
Common:	Flushing
Uncommon:	Hypotension
Rare:	Circulatory collapse
Respiratory, thoracic and mediastinal disorders	
Common:	Cough
Uncommon:	Dry throat*
Rare:	Oropharyngeal pain
Gastrointestinal disorders	
Uncommon:	Abdominal pain, constipation, dyspepsia*, nausea, tongue disorder*
Rare:	Lip oedema, diarrhoea, dry mouth, gingivitis
Hepatobiliary disorders	
Uncommon:	ALT increased, AST increased
Skin and sub-cutaneous tissue disorders	
Uncommon:	Erythema, angioedema*, swelling face*, dermatitis*, rash*, urticaria*
Musculoskeletal, connective tissue disorders	
Uncommon:	Arthralgia
Renal and urinary disorders	
Uncommon:	Pollakiuria, nocturia*, polyuria*
Reproductive System and Breast disorders	
Uncommon:	Erectile dysfunction*

General disorders and administration site conditions	
Uncommon:	Asthenia, fatigue, feeling hot, oedema peripheral, weakness*
Note: * Only in one patient	

Lercanidipine Monotherapy

About 1.8% of treated patients experienced adverse reactions.

The incidence of adverse drug reactions, at least possibly causally related, grouped by WHO-ART Body System classification, and ranked by frequency (uncommon, rare) is listed below.

The most commonly occurring adverse reactions reported in controlled clinical trials are headache, dizziness, peripheral oedema, tachycardia, palpitations, flushing, each occurring in less than 1% of patients.

Skin and Subcutaneous Tissue Disorders	
Uncommon:	rash, pruritus
Rare:	urticaria
Not known:	angioedema[1]
Musculoskeletal and Connective Tissue Disorders	
Uncommon:	myalgia
Nervous System Disorders	
Common:	headache
Uncommon:	dizziness
Rare:	somnolence, syncope
Gastrointestinal System Disorders	
Uncommon:	nausea; dyspepsia; abdominal pain upper
Rare:	vomiting, diarrhoea
Not known:	gingival hypertrophy[1], peritoneal cloudy effluent[1]
General Disorders and Administration Site Conditions	
Common:	oedema peripheral
Uncommon:	asthenia, fatigue
Rare:	chest pain
Cardiac Disorders	
Common:	tachycardia, palpitations
Rare:	angina pectoris

Vascular Disorders	
Common:	flushing
Uncommon:	hypotension
Renal and Urinary Disorders	
Uncommon:	polyuria
Rare:	pollakiuria
Immune System Disorders	
Rare:	hypersensitivity
Hepatobiliary Disorders	
Not known:	serum transaminase increased[1]

[1] adverse reactions from spontaneous reporting in the worldwide post-marketing experience

Some dihydropyridines may rarely lead to precordial pain or angina pectoris. Very rarely, patients with pre-existing angina pectoris may experience increased frequency, duration or severity of these attacks. Isolated cases of myocardial infarction may be observed. Lercanidipine does not appear to adversely influence blood sugar or serum lipid levels.

Cloudy peritoneal effluent (in patients on peritoneal dialysis) has been associated with lercanidipine use.

Additional information on the individual components

Adverse reactions reported with one of the individual components (enalapril or lercanidipine) may be potential undesirable effect with ZAN-EXTRA as well, even if not observed in clinical trials or during the post-marketing period.

Enalapril Monotherapy

Undesirable effects reported for enalapril include:

Blood and Lymphatic System Disorders	
Uncommon:	anaemia (including aplastic and haemolytic)
Rare:	neutropenia; decreases in haemoglobin; decreases in haematocrit; thrombocytopenia; agranulocytosis; bone marrow depression; pancytopenia; lymphadenopathy; autoimmune diseases
Endocrine Disorders	
Not known:	syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and Nutrition Disorders	
Uncommon:	hypoglycaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Hypoglycaemia)

Nervous System Disorders	
Very common:	dizziness
Common:	headache; syncope; taste alteration
Uncommon:	somnolence; paraesthesia; vertigo
Psychiatric Disorders	
Common:	depression
Uncommon:	confusion; nervousness; insomnia
Rare:	dream abnormality; sleep disorder
Eye Disorders	
Very common:	blurred vision
Cardiac Disorders	
Common:	myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Hypotension); chest pain; rhythm disturbances; angina pectoris; tachycardia
Uncommon:	palpitations
Vascular Disorders	
Common:	hypotension (including orthostatic hypotension)
Uncommon:	flushing, orthostatic hypotension
Rare:	Raynaud's phenomenon
Respiratory, Thoracic and Mediastinal Disorders	
Very common:	cough
Common:	dyspnoea
Uncommon:	rhinorrhoea; sore throat and hoarseness; bronchospasm/asthma
Rare:	pulmonary infiltrates; rhinitis; allergic alveolitis/eosinophilic pneumonia
Gastrointestinal Disorders	
Very common:	nausea
Common:	diarrhoea; abdominal pain
Uncommon:	ileus; pancreatitis; vomiting; dyspepsia; constipation; anorexia; gastric irritations; dry mouth; peptic ulcer

Rare:	stomatitis/aphthous ulcerations, glossitis
Very rare:	intestinal angioedema
Hepatobiliary Disorders	
Rare:	hepatic failure; hepatitis (either hepatocellular or cholestatic); hepatitis including necrosis; cholestasis (including jaundice)
Skin and Subcutaneous Tissue Disorders	
Common:	rash; hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Angioedema)
Uncommon:	diaphoresis; pruritus; urticaria; alopecia
Rare:	erythema multiforme; Stevens-Johnson syndrome; exfoliative dermatitis; toxic epidermal necrolysis; pemphigus; erythroderma
	fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.
Musculoskeletal, Connective Tissue and Bone Disorders	
Uncommon:	muscle cramps
Renal and Urinary Disorders	
Uncommon:	renal dysfunction; renal failure; proteinuria
Rare:	oliguria
Reproductive System and Breast Disorders	
Uncommon:	impotence
Rare:	gynaecomastia
General Disorders and Administration Site Conditions	
Very common:	asthenia
Common:	fatigue
Uncommon:	tinnitus; malaise; fever
Investigations	
Common:	hyperkalaemia; increases in serum creatinine
Uncommon:	increases in blood urea; hyponatraemia
Rare:	elevations of liver enzymes; elevations of serum bilirubin

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In the post-marketing experience, some cases of intentional overdose requiring hospitalisation were reported with administration of enalapril/lercanidipine at doses from 100 up to 1000 mg each. The reported symptoms of hypotension, bradycardia, restlessness, somnolence and flank pain. However, this could also be due to the concomitant administration of high doses of other drugs (e.g. beta-blockers). The most likely manifestations of ZAN-EXTRA overdose are hypotension and reflex tachycardia.

Symptoms of overdose with enalapril and lercanidipine alone:

The most prominent features of overdose reported with enalapril to date are marked hypotension (beginning some six hours after ingestion of the tablets), concomitant with blockade of the renin-angiotensin system, and stupor. Symptoms associated with overdose of ACE inhibitors may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough. Serum enalaprilat levels 100- and 200-fold higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of enalapril respectively.

In post-marketing experience, two cases of overdose were reported (lercanidipine 150 mg and 280 mg, respectively, ingested in attempts to commit suicide). The first patient developed sleepiness and was treated by gastric lavage. The second developed cardiogenic shock with severe myocardial ischaemia and mild renal failure and was treated with high-dose catecholamines, furosemide (frusemide), digitalis and parenteral plasma expanders. Both cases resolved without sequelae. As with other dihydropyridines, overdose might be expected to cause excessive peripheral vasodilatation with marked hypotension and reflex tachycardia. However, at very high doses, the peripheral selectivity may be lost, causing bradycardia and a negative inotropic effect. The most common ADRs associated to cases of overdose have been hypotension, dizziness, headache and palpitations.

Treatment of cases of overdose with enalapril and lercanidipine alone:

Limited data are available for overdose in humans. The most likely manifestation of overdosage would be hypotension, which can be treated, if necessary, by intravenous infusion of normal saline solution.

If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If the tablets were ingested recently, measures to eliminate enalapril should be taken (e.g. vomiting, gastric lavage, administration of absorbents or sodium sulfate). Enalaprilat may be removed from the general circulation by haemodialysis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be continuously monitored.

Several hypertensive patients in clinical studies have received as much as 80 mg of enalaprilat intravenously over a fifteen minute period. No adverse effects, other than those associated with recommended dosages, were observed.

In case of severe hypotension, bradycardia and unconsciousness, cardiovascular support could be helpful, with intravenous atropine for bradycardia. In view of the prolonged pharmacological effect of lercanidipine, it is essential that the cardiovascular status of patients who take an overdose is monitored for at least 24 hours. There is no information on the value of dialysis. Since the drug is highly lipophilic, it is most probable that

plasma levels are no guide to the duration of the period of risk and dialysis may not be effective. Patients in whom a moderate to severe intoxication is anticipated should be observed in a high-care setting.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

ZAN-EXTRA 10/10 and ZAN-EXTRA 10/20 are fixed combinations of the calcium channel blocker, lercanidipine, and the angiotensin converting enzyme inhibitor, enalapril. In Phase III clinical trials performed in patients not adequately controlled by lercanidipine or enalapril monotherapy, the combination produced an additive antihypertensive effect which reduced blood pressure to a greater extent than the individual components.

Pharmacodynamics

Lercanidipine is a calcium channel antagonist of the dihydropyridine group and inhibits the transmembrane influx of calcium into cardiac and smooth muscle. The mechanism of its antihypertensive action is due to a direct relaxant effect on vascular smooth muscle thus lowering total peripheral resistance. Lercanidipine has a prolonged antihypertensive activity because of its high membrane partition coefficient, and is devoid of negative inotropic effects due to its vascular selectivity. Vasodilatation induced by lercanidipine is gradual in onset so acute hypotension with reflex tachycardia has rarely been observed in hypertensive patients. The antihypertensive activity of lercanidipine is mainly due to its (S)-enantiomer.

Enalapril maleate is a prodrug which when administered orally is hydrolysed to release the active converting enzyme inhibitor, enalaprilat. The liver appears to be the main site for this conversion. Enalapril maleate is the maleate salt of enalapril, a derivative of two amino acids, L-alanine and L-proline. Angiotensin Converting Enzyme (ACE) is a peptidyl dipeptidase which catalyses the conversion of angiotensin I to the pressor substance angiotensin II. Enalaprilat inhibits ACE which results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreased aldosterone secretion.

ACE is identical to kininase II. Thus enalaprilat may also block the degradation of bradykinin, a potent vasodepressor peptide. However the role that this plays in the therapeutic effects of enalapril remains to be elucidated.

The mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, however enalapril is antihypertensive even in patients with low-renin hypertension.

Administration of enalapril to patients with hypertension results in a reduction of both supine and standing blood pressure without a significant increase in heart rate.

Symptomatic postural hypotension is infrequent. In some patients the development of optimal blood pressure reduction may require several weeks of therapy. Abrupt withdrawal of enalapril has not been associated with rapid increase in blood pressure.

Effective inhibition of ACE activity usually occurs 2 to 4 hours after oral administration of an individual dose of enalapril. Onset of antihypertensive activity was usually seen at one hour, with peak reduction of blood pressure achieved by 4 to 6 hours after administration. The duration of effect is dose-related. However, at recommended doses, antihypertensive and haemodynamic effects have been shown to be maintained for at least 24 hours.

In haemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of enalapril there was an increase in renal blood flow; glomerular filtration rate was unchanged. There was no evidence of sodium or water retention. However in patients with low pretreatment glomerular filtration rates, the rates were usually increased.

In short term clinical studies in diabetic and non-diabetic patients with renal disease, decreases in albuminuria and urinary excretion of IgG and total urinary protein were seen after the administration of enalapril.

Clinical Trials

Factorial Study (CPL2-0008)

In a multi-centre, randomised, double-blind, placebo-controlled, parallel group, factorial design study 663 patients with essential hypertension were randomised to receive an eight-week double-blind treatment with either placebo or an active treatment with enalapril maleate (5 or 10 mg), lercanidipine HCl (5, 10 or 20 mg), or one of six different combinations of both drugs. Primary efficacy endpoint was the change from baseline in trough sitting DBP (24±2h post-dose). Both ANCOVA and response surface analysis were performed.

The 10 mg and 20 mg doses of lercanidipine HCl were significantly superior to placebo, as was the 10 mg dose of enalapril maleate, while the 5 mg dose of both monotherapies were not superior to placebo. All the six combinations of lercanidipine plus enalapril (including the low dose combinations) were superior to placebo.

In the response surface analysis, the estimated mean change in SitDBP from baseline in the lercanidipine HCl 10 mg/enalapril maleate 10 mg group (-10.42 mm Hg, 95% CI 9.46 – 11.39) was significantly different from the lercanidipine HCl 10 mg group (-8.23 mm Hg, 95% CI 7.27-9.19) and it was close to significance when compared to the enalapril maleate 10 mg group (-8.78 mm Hg, 95% CI 7.58-9.98). In addition, this combination had a similar reduction to that observed in the lercanidipine HCl 20 mg group (-9.88 mm Hg, 95% CI 8.56 – 11.19). The normalization rate in the lercanidipine HCl 10 mg/ enalapril maleate 10 mg group (55%) was similar to that observed in the lercanidipine HCl 20 mg group (59%), whereas rates of 40% and 43% were observed in the lercanidipine HCl 10 mg and the enalapril maleate 10 mg groups, respectively. Treatment with this dose combination was well tolerated. The combination lercanidipine 10 mg/enalapril maleate 10 mg was therefore considered a reasonable alternative, both from the efficacy and the safety perspectives, to drug titration in patients not controlled by lercanidipine HCl 10 mg monotherapy. Its efficacy was then tested in the pivotal add-on trial in non-responders to lercanidipine HCl (CPL-0018).

The efficacy of the 10 mg/10 mg strength in patients whose blood pressure is not adequately controlled by enalapril 10 mg alone has not been tested. The dose combination lercanidipine HCl 10 mg/enalapril maleate 20 mg was instead chosen to be tested in the pivotal study in non-responders to enalapril maleate (CPL-0019), even if not previously included in the factorial study, because 20 mg is the usual maintenance dose of enalapril maleate. The efficacy of the 10 mg/20 mg strength in comparison with both monotherapies and placebo was tested in study IT-CL 0044.

The lowest effective dose has not been formally determined.

Study IT-CL 0044

A double-blind, placebo-controlled, four-way balanced-design cross-over study, including patients aged 60 - 85 years with a mean office SitSBP of 160-179 mmHg and a daytime SBP ≥ 135 mmHg, was performed to evaluate whether combination therapy with lercanidipine and enalapril 10 mg/20 mg was more effective than either drug alone in reducing SBP in the elderly.

After a two week run-in period, during which previous medications were discontinued, each patient received the following four treatments in randomised order for four weeks each: lercanidipine 10 mg, enalapril 20 mg, the combination L10/E20 mg and placebo. 75 patients (40 males, mean age 66 years, office BP 168/92 mmHg,

daytime SBP 151 mmHg) were randomised, 72 entered in the ITT analysis and 62 completed the study with 4 valid post-baseline ABPMs and entered in the primary analysis on the PP population.

Administration of placebo, lercanidipine, enalapril and the combination was associated with mean 24-h SBP of 144, 137, 133 and 127 mmHg, respectively. All active treatments significantly reduced the mean 24-h SBP in comparison with placebo, but the combination L10/E20 mg was significantly more effective than lercanidipine 10 mg and enalapril 20 mg alone. Similarly, office SBP at trough was significantly more reduced with the combination (-16.9 mmHg) than with lercanidipine (-5.0 mmHg) or enalapril (-5.9 mmHg) monotherapies. A blood pressure < 140/90 mmHg was recorded in 18% of patients with lercanidipine, 19% with enalapril and 45% with L10/E20 mg. Combination therapy improved blood pressure control over monotherapies in the entire 24-hour period.

Tolerability of the combination therapy was good and no serious adverse reactions occurred.

Efficacy in Non-responders to Lercanidipine (CPL1-0018)

In a randomised, double blind study with 337 patients (in ITT population) whose blood pressures were inadequately controlled (DBP ≥ 95 mmHg) after 4 weeks treatment with lercanidipine 10 mg, patients were randomised to receive combination lercanidipine 10 mg and enalapril 10 mg once daily or lercanidipine 10 mg monotherapy for 12 weeks. Primary efficacy endpoint was the change from baseline in trough SitDBP (24±2h post-dose). Secondary efficacy parameters included the change from baseline in trough SitSBP and the percent of patients normalised or responders. At end of study, patients who used combination therapy were found to have a significantly greater reduction in trough SitSBP and SitDBP compared with those on monotherapy (-7.7 +/- 1.05 / -7.1 +/- 0.63 mmHg vs. -2.3 +/- 1.03 / -4.3 +/- 0.62 mmHg respectively). The statistically significant difference between treatment groups ($p< 0.001$) for reduction of both SitSBP and SitDBP were evident from as early as week 2 and persisted throughout the treatment period. It is noteworthy that the difference between treatments was even greater on SitSBP (5.4 mmHg) than on SitDBP (2.8 mmHg). SBP is recognised as the most important predictor of stroke and coronary mortality across all ages.

A significantly higher percentage of patients on combination treatment experienced normalisation of SitDBP (29% vs. 19%, $p=0.023$), SSBP (39% vs. 22%, $p<0.001$) or both (22% vs. 12%, $p=0.012$) compared with patients on monotherapy. The responder rate for both SitDBP and SitSBP was also significantly higher in patients treated with combination therapy compared with monotherapy (35% vs 24%, $p=0.032$ for SitDBP and 41% vs 24%, $p<0.001$ for SitSBP). The relatively low normalisation rates observed in this study were mainly due to the high blood pressure levels used as entry criteria. The SitSBP/SitDBP at baseline prior to randomisation to combination therapy was 152 ± 11/100 ± 3 mmHg. Higher normalisation rates would be expected in a patient group with lower blood pressure at baseline. The combination therapy was well tolerated.

Efficacy in Non-responders to Enalapril (Study CPL 1-0019)

In a randomised, double blind study, 327 patients (in ITT population) who were non-responders to enalapril (SitDBP ≥95 mmHg) after 2 weeks treatment with enalapril 10 mg followed by enalapril 20 mg for 4 weeks were randomised to 12 weeks' treatment with either monotherapy (enalapril 20 mg) or combination therapy (enalapril 20 mg + lercanidipine 10 mg) once daily. Primary efficacy endpoint was the change from baseline in trough SitDBP (24±2h post-dose). Secondary efficacy parameters included the change from baseline in trough SitSBP and the percent of patients normalised or responders. At study end, patients on combination therapy achieved significantly greater reduction in trough SitDBP compared with monotherapy (-9.2 +/- 0.64 vs. -7.5 +/- 0.64 mmHg respectively, $p=0.015$). The difference in SitDBP reduction between treatments was 1.8 mmHg. The significant difference between treatments was evident at week 8 and persisted through the whole treatment period. Similarly, patients on combination therapy were found to have significantly greater reduction in trough SitSBP compared with those on monotherapy (-9.8 +/- 1.11 vs. -6.7 +/- 1.11 mmHg respectively, $p=0.013$). The difference in SitSBP reduction between treatments was 3.1 mmHg. The significant difference was evident at week 4 and persisted to study end.

A higher percentage of patients on combination therapy experienced normalisation of SitDBP compared with patients on monotherapy (48% vs. 37%, p=0.055). Higher responder rates were also observed in patients on combination therapy for SitDBP (53% vs. 43%) and SitSBP (41% vs. 33%), even if these differences did not reach the conventional level of statistical significance (p=0.076 and p=0.116, respectively).

Elderly Patients

Since approximately 50% of the patients in the CPL 1-0019 study (164/327) were at least 60 years of age, a post-hoc subgroup analysis was performed at endpoint in the subgroup aged ≥60 years and also in the smaller subgroup (n=101) aged ≥65 years:

In patients aged ≥60 years, combination therapy showed a significantly greater decrease from baseline in trough SitDBP at endpoint compared with monotherapy (-10.9 ± 0.86 mmHg vs. -7.9 ± 0.85 mmHg, p=0.002). The decrease from baseline in trough SitSBP at endpoint was -10.7 ± 1.43 mmHg for combination therapy and -7.5 ± 1.43 mmHg for monotherapy, p=0.054.

In patients aged ≥65 years, a greater decrease in SitDBP and SitSBP from baseline at endpoint was seen in the combination therapy group. The treatment difference for SitDBP (3.2 mmHg) was statistically significant (p=0.044), despite the small sample size.

Long-term Efficacy

Open-label long-term extension of the randomised, double-blind add-on studies were conducted to extend treatment data up to 6 and 12 months (including the original 3 months randomised phase). In both studies the improvements in blood pressure control obtained with combination therapy during the double-blind phase of the study were maintained or increased during the long-term treatment up to 12 months duration.

In non-responders to enalapril, all the 186 patients who entered the open label phase of study CPL1-0019 were treated with lercanidipine 10 mg / enalapril 20 mg. At the last visit 60% of these patients had a SitDBP <90 mmHg and 36% a BP <140/90 mmHg.

In non-responders to lercanidipine, all patients (n=221) who entered the open-label phase of study CPL1-0018 were initially treated with lercanidipine 10 mg/enalapril 10 mg, but titration to lercanidipine 10 mg / enalapril 20 mg was allowed during this phase if BP remained >140/90 mmHg. At the last visit 46% of all the patients who entered the open-label extension had a SitDBP <90 mmHg and 37% a BP <140/90 mmHg. Titration occurred in 133 patients, and SitDBP (or SitSBP) normalised after titration in about 1/3 of the cases. The improvements in blood pressure control were not obtained at the expense of tolerability.

5.2 PHARMACOKINETIC PROPERTIES

When lercanidipine and enalapril were administered concomitantly, no pharmacokinetic interaction was observed.

Lercanidipine

Absorption

Lercanidipine is completely absorbed after oral administration and peak plasma levels occur about 1.5 to 3 hours after dosing.

The two enantiomers of lercanidipine show a similar plasma level profile: The time to peak plasma concentration is the same, the peak plasma concentration and AUC are, on average, 1.2-fold higher for the (S)-enantiomer. No *in vivo* interconversion of enantiomers is observed.

The absolute bioavailability of lercanidipine is about 10%, because of high first pass metabolism. The bioavailability increases 4-fold when lercanidipine is ingested up to 2 hours after a high fat meal, and about 2-fold when taken immediately after a carbohydrate-rich meal. Consequently, lercanidipine should be taken at least 15 minutes before a meal.

Distribution

Distribution from plasma to tissues and organs is rapid and extensive.

The degree of serum protein binding of lercanidipine exceeds 98%. Since plasma protein levels are reduced in patients with severe renal or hepatic dysfunction, the free fraction of the drug may be increased.

Metabolism

Lercanidipine is extensively metabolised by CYP3A4; no parent drug is found in the urine or the faeces. It is predominantly converted to inactive metabolites and about 50% of the dose is excreted in the urine.

Oral administration of lercanidipine leads to plasma levels not directly proportional to dosage (non-linear kinetics). After 10, 20 or 40 mg, peak plasma concentrations observed were in the ratio 1:3:8 and areas under plasma concentration time curves in the ratio 1:4:18, suggesting a progressive saturation of first pass metabolism. Thus, availability increases with dosage elevation.

Excretion

Elimination occurs essentially by biotransformation.

The mean terminal elimination half-life of S- and R-lercanidipine enantiomers is 5.8 ± 2.5 and 7.7 ± 3.8 hours respectively. No accumulation was seen upon repeated administration. The therapeutic activity lasts for 24 hours because of its high binding to lipid membranes.

Elderly, Renal Impairment and Hepatic Impairment

In elderly patients and in patients with mild to moderate renal dysfunction or mild to moderate hepatic impairment, the pharmacokinetic behaviour of lercanidipine was shown to be similar to that observed in the general patient population; patients with severe renal dysfunction or dialysis-dependent patients showed higher levels (about 70%) of the drug. In patients with moderate to severe hepatic impairment, the systemic bioavailability of lercanidipine is likely to be increased since the drug is normally metabolised extensively in the liver.

Enalapril

Absorption

Oral enalapril is rapidly absorbed with peak serum concentrations occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril tablets is approximately 60%, similar for the various doses in the therapeutic range. The absorption of oral enalapril is not influenced by the presence of food in the gastrointestinal tract.

Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor.

Peak concentration of enalaprilat occurs three to four hours after an oral dose of enalapril maleate.

Distribution

Approximately 50% of enalaprilat is bound to plasma proteins. The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently associated with binding to ACE. In subjects with normal renal function, steady state serum concentrations of enalaprilat were achieved by the fourth day of administration of enalapril maleate. The plasma concentration time profile of enalaprilat was complex with several exponentials including a very prolonged terminal phase (t1/2 >30 hours). The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril maleate is eleven hours.

Metabolism

Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril. The extent of hydrolysis of enalapril is similar for the various doses in the recommended therapeutic range.

Excretion

Excretion of enalaprilat is primarily renal. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril (about 20%).

Renal Impairment

The exposure of enalapril and enalaprilat is increased in patients with renal insufficiency. In patients with mild to moderate renal insufficiency (GFR 40-60 mL/min) steady state AUC of enalaprilat was approximately two-fold higher than in patients with normal renal function after administration of 5 mg once daily. In severe renal impairment (GFR ≤30 mL/min) AUC was increased approximately 8-fold. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency and time to steady state is delayed (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

There was no evidence of genotoxic activity for lercanidipine or enalapril. Lercanidipine did not induce gene mutation (*S. typhimurium* or Chinese hamster V79 fibroblasts), gene conversion (*Saccharomyces ceresvisiae* D4) or chromosomal damage (CHO cytogenetic assay; mouse micronucleus test).

Neither enalapril maleate nor the active diacid was mutagenic in the Ames test with *S. typhimurium*. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and chromosome aberration and micronucleus tests in mice.

Carcinogenicity

Carcinogenicity studies using the lercanidipine+enalapril combination have not been performed.

Lercanidipine

Carcinogenicity studies of lercanidipine administered via the diet have been performed in rats and mice (18 months), using doses up to 60 mg/kg/day for mice and 5 mg/kg/day for rats. Plasma concentrations (AUC) of lercanidipine at the highest doses were about 4-8 times the AUC expected in humans at 10 mg/day. Lercanidipine showed no evidence of carcinogenic activity in these studies.

Enalapril

There was no evidence of carcinogenicity when enalapril was administered to rats for 106 weeks at doses up to 90 mg/kg/day or to male and female mice for 94 weeks at doses up to 90 and 180 mg/kg/day, respectively.

Several ACE inhibitors have been associated with an increase in the incidence of oxyphilic renal tubular cells and oncocytomas in rats. The potential for ACE inhibitors to cause this effect in humans is unknown. The progression of oxyphilic cells to oncocytomas is rare in humans and when it does occur, it is considered benign.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ZAN-EXTRA film-coated tablets contain the following excipients:

Lactose monohydrate, microcrystalline cellulose, sodium starch glycollate Type A, povidone, sodium bicarbonate, magnesium stearate, hypromellose, titanium dioxide, purified talc, macrogol 6000.

Additionally, ZAN-EXTRA 10/20 film-coated tablets contain quinoline yellow aluminium lake and iron oxide yellow.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: blister pack (polyamide-aluminium-PVC/aluminium)

Pack sizes: 7 (sample), 10 (sample), 14, 28, 30, 35, 50, 56, 60, 98 and 100

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 120955 – ZAN-EXTRA 10/10 lercanidipine hydrochloride 10 mg and enalapril maleate 10 mg film coated tablets blister pack

AUST R 120961 – ZAN-EXTRA 10/20 lercanidipine hydrochloride 10 mg and enalapril maleate 20 mg film coated tablets blister pack

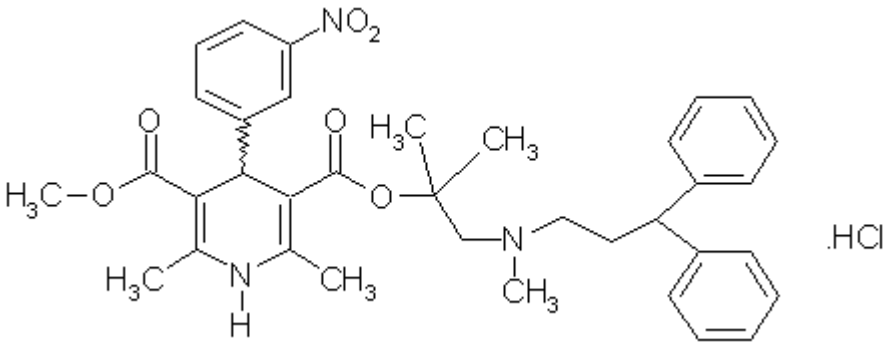
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Lercanidipine HCl

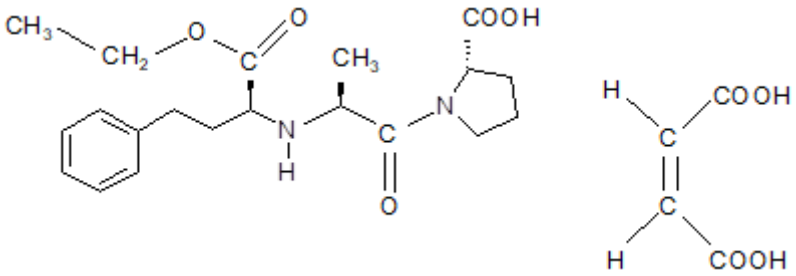


Chemical name: 3,5-pyridinedicarboxylic acid, 1,4- dihydro-2, 6-dimethyl-4-(3-nitrophenyl)-2-[(3,3-diphenylpropyl)methylamino]-1,1-dimethylethyl methyl ester hydrochloride

Molecular weight: 648.2 (Free base: 611.7)

Lercanidipine hydrochloride is a microcrystalline, odourless, citrine-coloured powder, readily soluble in chloroform and methanol, practically insoluble in water. Octanol:water partition coefficient (LogP): 6.4.

Enalapril maleate



Chemical name: (2S)-1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]pyrrolidine-2-carboxylic acid (Z)-butenedioate

Molecular weight: 492.5

Enalapril maleate is a white or almost white crystalline powder sparingly soluble in water, practically insoluble in dichloromethane, and freely soluble in methyl alcohol. It dissolves in dilute solutions of alkali hydroxides. A 1% solution in water has a pH of 2.4 to 2.9.

CAS Number

Lercanidipine HCl: 132866-11-6

Enalapril maleate: 76095-16-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

31/01/2008

10 DATE OF REVISION

20/02/2023

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.2	Inclusion of grapefruit interactions
4.3	Addition of contraindications

4.4	Addition of warnings
4.5	Addition of interactions
4.6	Addition of warnings for use in males and other warnings
4.8	Addition and updated frequency of adverse effects
4.9	Addition of warnings for overdose

ZAN-EXTRA_pi\Feb23/01 (CCDS 27-Jul-2019)