

## **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 is available as tablets of two separate strengths, ZAN-EXTRA 10/10 and ZAN-EXTRA 10/20 both containing lercanidipine hydrochloride 10 mg and enalapril maleate either 10 mg or 20 mg respectively.

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.

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 10mg/10mg tablets versus enalapril 10mg 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.

### Use in the Elderly

The dose for elderly patients should be in line with their renal function (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Use in Renal Dysfunction).

### Use in Children

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

### Use in Renal Dysfunction

ZAN-EXTRA is contraindicated in severe renal impairment (creatinine clearance <30 mL/min) or in patients on haemodialysis (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Special care should be exercised when treatment is commenced in patients with mild to moderate impairment of kidney function.

### Use in Hepatic Dysfunction

ZAN-EXTRA is contraindicated in severe hepatic impairment. Special care should be exercised when treatment is commenced in patients with mild to moderate impairment of liver function.

## 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 (creatinine clearance < 30 mL/min).
- 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)
- History of angioedema whether hereditary or idiopathic, or associated with previous ACE inhibitor therapy.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

### **Angioedema**

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril maleate. 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.

The risk of angioedema may be increased in patients taking an ACE inhibitor and concomitant vildagliptin (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

### **Hypotension**

Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis [see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. In patients with heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotaemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the early weeks of treatment with ZAN-EXTRA and whenever the dose of enalapril is increased. 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.

### **Neutropenia/Agranulocytosis**

Another angiotensin converting enzyme inhibitor has been shown to cause agranulocytosis and bone marrow depression (including leucopenia/neutropenia). These reports generally involve patients who have pre-existing renal dysfunction and/or collagen vascular disease, some of whom have received concomitant immunosuppressant therapy. Most reports describe transient episodes for which a causal relationship to the ACE inhibitor could not be established. 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. *Exp. Opin. Invest. Drugs 1999;8:1043-1062*] 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 tended to prolong the PR interval [A. Cavallini and G. Terzi; Effects of antihypertensive therapy with lercanidipine and verapamil on cardiac electrical activity in patients with hypertension: a randomised, double-blind pilot study. *Curr Ther Res Clin Exp.* 2000;61:477-487 (ID186)].

### **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.

### **Outflow Obstruction (Aortic Stenosis)**

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.

### **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)].

### **Inducers of CYP3A4**

Inducers of CYP3A4 like anticonvulsants (e.g. phenytoin, carbamazepine) and rifampicin may reduce lercanidipine's plasma levels and therefore the efficacy of lercanidipine may be less than expected (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

### **Aortic or Mitral Valve Stenosis/Hypertrophic Cardiomyopathy**

As with all vasodilators, 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.

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

The use of an ACE inhibiting drug (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 serum creatinine, 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.

### **Angioedema**

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).

### **Anaphylactoid Reactions During Hymenoptera Desensitization**

Rarely, patients receiving ACE inhibitors during desensitization 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 desensitization or apheresis.

### **Haemodialysis Patients**

Anaphylactoid reactions have been reported in patients dialyzed 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 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 percent 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.

## 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 people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population (see SECTION 5.1 PHARMACODYNAMIC PROPERTIES).

## Alcohol

Alcohol should be avoided since 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).

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 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).

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

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, usually minor and transient especially when enalapril has been given concurrently with a diuretic. Discontinuation of the diuretic, or of ZAN-EXTRA because of the enalapril component, 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 (cross reference to ciclosporin use).

### **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 (creatinine clearance < 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.

### **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 enhanced when associated with other antihypertensive drugs such as diuretics, beta-blockers, alpha-blockers and others.

The following interactions may be observed with one or the other component of the combination.

### **Lercanidipine**

#### **Inhibitors and Inducers of CYP3A4**

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

Therefore, inhibitors of CYP3A4 (such as ketoconazole, itraconazole, erythromycin, ritonavir and fluoxetine) may increase the plasma concentration of lercanidipine, and such combinations should be used with caution.

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

### 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 and quinidine).

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.

Moreover, interaction studies in humans have shown that lercanidipine did not modify the plasma levels of metoprolol (a typical substrate of CYP2D6). Therefore, at therapeutic doses, it is unlikely that lercanidipine will inhibit the biotransformation of drugs metabolised by CYP2D6.

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<sub>50</sub> of 2.6 µm and 0.8 µm, respectively). The IC<sub>50</sub> 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.

### Beta-blockers

When lercanidipine was administered with metoprolol, a beta-blocker eliminated mainly by the liver, the bioavailability of metoprolol was not changed, while that of lercanidipine was reduced by 50%. Therefore, when co-administered with metoprolol, it may be necessary to increase the dose of lercanidipine. It is anticipated that a similar effect may occur with propranolol.

### Cardiac glycosides

Co-administration of lercanidipine in patients chronically treated with beta-methyl digoxin (a pro-drug of digoxin) showed no evidence of a pharmacokinetic interaction. However, patients on concomitant digoxin treatment should be closely monitored.

### Cimetidine

Concomitant administration of cimetidine 400 mg BD does not cause significant changes in the plasma levels of lercanidipine: AUC and C<sub>max</sub> 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

See Section 5.2 PHARMACOKINETIC PROPERTIES.

The metabolism of dihydropyridines can be inhibited by grapefruit juice, leading to increased plasma concentration and hypotensive effect.

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

### Ciclosporin

Ciclosporin and lercanidipine should not be administered together (see Section 4.3 CONTRAINDICATIONS and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS – CYP3A4 and CYP2D6 substrates).

### Warfarin

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

### **Enalapril**

#### Potassium-sparing diuretics or potassium supplements

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. 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. 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).

#### Agents causing renin release

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

#### 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.

#### Lithium

As with other drugs which eliminate sodium, lithium clearance may be reduced. 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).

#### 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 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 ACE inhibitors may result in a further deterioration of renal function, including possible renal failure. These effects are usually reversible.

These interactions should be considered in patients taking NSAIDs including COX-2 inhibitors concomitantly with diuretics and ACE inhibitors. Therefore, such a combination should be administered with caution, especially in the elderly.

### 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.

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.

### Vildagliptin

Coadministration of an ACE inhibitor and vildagliptin may increase the risk of angioedema (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

## **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 Pregnancy**

Pregnancy Category: D

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

Pregnancy should be excluded before starting treatment with enalapril and avoided during treatment.

If a patient intends to become pregnant while on enalapril, 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 foetal 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 foetus. ACE inhibitors have also been associated with foetal death *in utero*.

There is a potential risk of foetal hypertension, decreased birth weight and decreased renal perfusion or anuria in the foetus from *in utero* exposure to ACE inhibitors. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the foetus. 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 foetal toxicity occurred in some rabbits at doses equal to or greater than 1 mg/kg/day. Saline supplementation prevented the maternal and foetal 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 foetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril. Foetotoxicity shown as decreased average foetal weight, occurred in rats given 1,200 mg/kg/day of enalapril, but did not occur when these animals were supplemented with saline.

### **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 it is unlikely to impair 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.

**Table 1**

	<b>ZAN-EXTRA 10/10</b>		<b>ZAN-EXTRA 10/20</b>	
Frequency System organ Class	<b>Common (1.0 – 10%)</b>	<b>Uncommon (0.1 – 1.0%)</b>	<b>Common (1.0 – 10%)</b>	<b>Uncommon (0.1 – 1.0%)</b>
Blood and lymphatic system disorders				Thrombocytopenia
Metabolism and nutrition disorders				Hypertriglyceridaemia*
Psychiatric disorders				Anxiety*
Immune system disorders		Hypersensitivity*		
Nervous system disorders	Dizziness	Headache Loss of consciousness*	Headache Dizziness (including postural dizziness)	
Ear and labyrinth disorders	Vertigo			
Cardiac disorders		Palpitations Tachycardia*		Palpitations
Vascular disorders		Hypotension*	Flushing	Hypotension*
Respiratory, thoracic and mediastinal disorders	Cough	Dry throat*	Cough	Pharyngolaryngeal pain*
Gastrointestinal disorders		Abdominal pain upper* Nausea*		Abdominal pain Constipation* Dyspepsia* Nausea* Tongue disorder*
Skin and sub-cutaneous tissue disorders		Dermatitis* Erythema* Face oedema* Urticaria*		Angioneurotic oedema* Erythema* Rash*
Musculoskeletal, connective tissue disorders		Arthralgia*		Arthralgia*
Renal and urinary disorders		Polyuria* Urinary frequency*		Nocturia*
Reproductive system and breast disorders		Erectile dysfunction*		
General disorders and administration site conditions		Fatigue Weakness*	Oedema peripheral	Asthenia* Fatigue Feeling hot* Weakness*
Investigations		Haemoglobin decreased		Alanine aminotransferase increased Aspartate aminotransferase increased

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 Appendages Disorders*

Rare: rash

#### *Musculoskeletal System Disorders*

Rare: myalgia

#### *Central & Peripheral Nervous System Disorders*

Uncommon: headache; dizziness

#### *Psychiatric Disorders*

Rare: somnolence

#### *Gastro-intestinal System Disorders*

Rare: nausea; dyspepsia; diarrhoea; abdominal pain; vomiting

#### *Cardiovascular Disorders, General*

Uncommon: oedema peripheral

#### *Myo-, Endo- Pericardial & Valve Disorders*

Rare: angina pectoris

#### *Heart Rate and Rhythm Disorders*

Uncommon: tachycardia; palpitations

#### *Vascular (Extracardiac) Disorders*

Uncommon: flushing

#### *Urinary System Disorders*

Rare: polyuria

#### *Body as a whole – General Disorders*

Rare: asthenia; fatigue

### Post-marketing experience

In post-marketing experience, from spontaneous reports the following undesirable effects were reported very rarely (<1/10,000 or 0.01%): gingival hypertrophy, reversible increases in serum levels of hepatic transaminases, hypotension, urinary frequency and chest pain.

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.

### Enalapril monotherapy

Undesirable effects reported for enalapril include:

*Blood and the Lymphatic System Disorders*

Uncommon: anaemia (aplastic and haemolytic)

Rare: neutropenia; decreases in haemoglobin; decreases in haematocrit; thrombocytopenia; agranulocytosis; bone marrow depression; pancytopenia; lymphadenopathy; autoimmune diseases

*Metabolism and Nutrition Disorders*

Uncommon: hypoglycaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Hypoglycaemia)

*Nervous System and Psychiatric Disorders*

Common: headache; depression

Uncommon: confusion; somnolence; insomnia; nervousness; paraesthesia; vertigo

Rare: dream abnormality; sleep disorder

*Eye Disorders*

Very common: blurred vision

*Cardiac and Vascular Disorders*

Very common: dizziness

Common: hypotension (including orthostatic hypotension); syncope; 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: orthostatic hypotension; palpitations

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

*Gastro-intestinal Disorders*

Very common: nausea

Common: diarrhoea; abdominal pain; taste alteration

Uncommon: ileus; pancreatitis; vomiting; dyspepsia; constipation; anorexia; gastric irritations; dry mouth; peptic ulcer

Rare: stomatitis/aphthous ulcerations, glossitis

*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

A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

### *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: muscle cramps; flushing; 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](http://www.tga.gov.au/reporting-problems).

## **4.9 OVERDOSE**

At this stage, no cases of overdose with the combination tablet ZAN-EXTRA have been reported.

The most likely manifestations of ZAN-EXTRA overdose are hypotension and reflex tachycardia.

### **Overdose - Experience with lercanidipine**

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. 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.

### **Overdose – Experience with enalapril**

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. 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. Enalaprilat may be removed from the general circulation by haemodialysis.

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 catalyzes 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.

#### Ethnic differences

As with other ACE inhibitors, enalapril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

### **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  $\geq$  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 yrs, 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  $\geq$  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 $\pm$ 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  $\pm$  1.05 / -7.1  $\pm$  0.63 mmHg vs. -2.3  $\pm$  1.03 / -4.3  $\pm$  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 normalization 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 normalization 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 randomization to combination therapy was  $152 \pm 11/100 \pm 3$  mmHg. Higher normalization 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  $\geq 95$  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 $\pm$ 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 ( $-9.2 \pm 0.64$  vs.  $-7.5 \pm 0.64$  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 ( $-9.8 \pm 1.11$  vs.  $-6.7 \pm 1.11$  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 normalization 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  $\geq 60$  years and also in the smaller subgroup ( $n=101$ ) aged  $\geq 65$  years:

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

In patients aged  $\geq 65$  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 10mg / enalapril 20mg. 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  $5.8 \pm 2.5$  and  $7.7 \pm 3.8$  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 ( $t_{1/2} >30$  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 (creatinine clearance 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 (creatinine clearance  $\leq 30$  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 cerevisiae* 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 glycolate 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**

ZAN-EXTRA 10/10 tablets are available in packs of 7 (physician's sample), 10 (physician's sample), 14, 28, 30, 35, 50, 56, 60, 98 and 100 tablets.

ZAN-EXTRA 10/20 tablets are available in packs of 7 (physician's sample), 10 (physician's sample), 14, 28, 30, 35, 50, 56, 60, 98 and 100 tablets.

ZAN-EXTRA tablets are packaged in polyamide-aluminium-PVC/aluminium blisters, inside cardboard cartons.

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

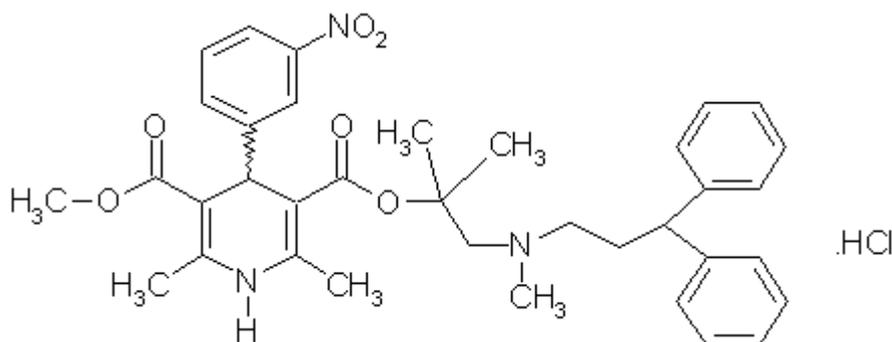
## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

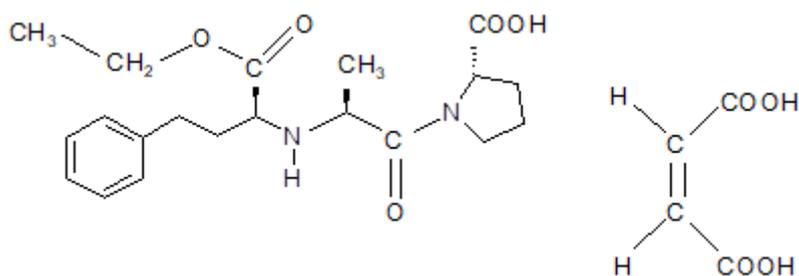
#### Lercanidipine HCl



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)

#### Enalapril maleate



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

Molecular Weight: 492.5

### CAS Number

Lercanidipine HCl: 132866-11-6

Enalapril maleate: 76095-16-4

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 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.

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

## 8 SPONSOR

**Viatrix Pty Ltd**

Level 1, 30 The Bond

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Millers Point NSW 2000

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Phone: 1800 274 276

## 9 DATE OF FIRST APPROVAL

31/01/2008

## 10 DATE OF REVISION

21/01/2022

### Summary Table of Changes

Section Changed	Summary of New Information
2	Revision of Schedule 1 declaration
6.1	Minor editorial change
6.5	Insert AUST R numbers; Minor editorial change
8	Update sponsor's details

ZAN-EXTRA® is a Viatrix company trade mark

ZAN-EXTRA\_pi\Jan22/01