SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zaneril 20 mg/10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg enalapril maleate (equivalent to 15.29 mg enalapril) and 10 mg lercanidipine hydrochloride (equivalent to 9.44 mg lercanidipine).

Excipients with known effect:
each tablet contains 92.0 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Yellow, circular, biconvex tablets of 8.5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in patients whose blood pressure is not adequately controlled by enalapril 20 mg alone.
Fixed combination Zaneril 20 mg/10 mg should not be used for initial treatment of hypertension.

4.2 Posology and method of administration

Patients whose blood pressure is not adequately controlled by treatment with enalapril 20 mg alone could either be titrated up to the higher dose of enalapril monotherapy or switched to Zaneril 20mg/10mg.
Individual dose titration with the components can be recommended. When clinically appropriate, direct switch from monotherapy to the fixed combination may be considered.

Posology
The recommended dose is one tablet once a day at least 15 minutes before meals.

Elderly:
The dose should depend on the patient's renal function (see "Use in renal impairment").

Renal impairment:
Zaneril is contraindicated in patients with severe renal dysfunction (creatinine clearance <30 ml/min) or in patients undergoing haemodialysis (see section 4.3 and 4.4). Particular caution is needed when initiating treatment in patients with mild to moderate renal dysfunction.

Hepatic impairment:
Zaneril is contraindicated in severe hepatic dysfunction. Particular caution is needed when initiating treatment in patients with mild to moderate hepatic dysfunction.

Paediatric population
There is no relevant use of Zaneril in the paediatric population for the indication of hypertension.

Method of administration
Precautions to be taken before handling or administering the medicinal product:
- Treatment should be preferably administered in the morning at least 15 minutes before breakfast.
- This product should not be administered with grapefruit juice (see section 4.3 and 4.5).

4.3 Contraindications

- Hypersensitivity to any ACE-inhibitor or dihydropyridine calcium channel blocker or to any of the excipients listed in section 6.1.
- History of angioedema associated with ACE-inhibitor therapy.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Left ventricular outflow tract obstruction.
- Untreated congestive cardiac failure.
- Unstable angina pectoris or recent (within 1 month) myocardial infarction.
- Severe hepatic impairment.
- Severe renal impairment (GFR < 30 ml/min), including patients undergoing dialysis.
- Co-administration with:
  - strong CYP3A4 inhibitors (see section 4.5)
  - ciclosporin (see section 4.5)
  - grapefruit or grapefruit juice (see section 4.5)
- Concomitant use with sacubitril/valsartan therapy. Enalapril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

The concomitant use of Zaneril with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Symptomatic hypotension

Symptomatic hypotension is 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). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. 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. In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of enalapril and/or diuretic is adjusted. Similar considerations may apply to patients with ischemic 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 the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually 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 systematic 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 of dose and/or discontinuation of the diuretic and/or enalapril may be necessary.

Sick-sinus syndrome
Lercanidipine should be administered with caution in patients with sick-sinus syndrome (without a pacemaker).

Left ventricular dysfunction
Although haemodynamic controlled studies revealed no impairment of ventricular function, care is required in patients with left ventricular dysfunction.

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. 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 (see section 4.8).

Renal impairment
Particular caution is required with enalapril when initiating treatment in patients with mild to moderate renal impairment. Routine monitoring of serum potassium and creatinine are part of the 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 therapy with enalapril treatment is usually reversible.
Some hypertensive patients, with no apparent pre-existing renal disease, have developed increases in blood urea and creatinine when enalapril has been given

concurrently with a diuretic. Dosage 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, Renovascular hypertension).

Renovascular hypertension
There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE-inhibitor. 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 and cautious titration and monitoring of renal function.

Kidney transplantation
There is no experience in the use of lercanidipine or enalapril in patients who have recently undergone kidney transplantation. Treatment with Zaneril is therefore not recommended.

Hepatic failure
The antihypertensive effect of lercanidipine can be potentiated in patients with hepatic dysfunction.
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 elevation of hepatic enzymes should discontinue the ACE-inhibitor and receive appropriate medical follow up.

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.

Neutropenia/agranulocytosis
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE-inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. 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. Some of these patients developed severe infections which in few instances did not respond to intensive antibiotic therapy. If enalapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any signs of infection.

Hypersensitivity/angioneurotic oedema
Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx, has been reported in patients treated with ACE-inhibitors, including enalapril. This may occur at any time during treatment. In such cases, enalapril should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. 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 epinephrine solution 1:1000 (0.3ml to 0.5ml) and/or measures to ensure a patent airway, should be administered promptly.
Black patients receiving ACE-inhibitors have been reported to have a 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).
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 sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, 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). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

Anaphylactoid Reactions during Hymenoptera Desensitisation
Rarely, patients receiving ACE-inhibitors during desensitisation with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each desensitisation.

Anaphylactoid Reactions during LDL-Apheresis
Rarely, patients receiving ACE-inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

Hypoglycaemia
Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE-inhibitor, should be told to closely monitor for hypoglycaemia, especially during the first month of combined use (see section 4.5).

Cough
Cough has been reported with the use of ACE-inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE-inhibitor-induced cough should also be considered as part of the differential diagnosis of cough.

Surgery/anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, enalapril blocks 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.

Serum potassium
ACE inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalaemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5).

Lithium
The combination of lithium and enalapril is generally not recommended (see section 4.5).

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 sections 4.5 and 5.1).
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.

Inducers of CYP3A4
Inducers of CYP3A4 such as anticonvulsants (e.g. phenytoin, carbamazepine) and rifampicin may reduce lercanidipine plasma levels and therefore the efficacy of lercanidipine may be less than expected (see section 4.5).

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.

Pregnancy
Zaneril is not recommended during pregnancy.

ACE-inhibitors, like enalapril, should not be initiated during pregnancy. Unless continued ACE-inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE-inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

The use of lercanidipine is also not recommended during pregnancy or in women who might become pregnant (see section 4.6).

Lactation
The use of Zaneril is not recommended during lactation (see section 4.6).

Paediatric population
The safety and efficacy of this association has not been demonstrated in children.

Alcohol
Alcohol should be avoided because it may potentiate the effect of vasodilating antihypertensive drugs (see section 4.5).

Lactose
This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take Zaneril.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

The antihypertensive effect of Zaneril could be potentiated by other blood pressure-lowering drugs such as diuretics, beta-blockers, alpha-blockers and other substances.

In addition, the following interactions have been observed with one or other constituents of the combined product.

Enalapril maleate

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 and 4.4).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the 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 RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with enalapril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also 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. Therefore, the combination of enalapril with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

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.

Diuretics (thiazides or loop diuretics)
Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating treatment with enalapril (see section 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of enalapril.

Other antihypertensive agents
Concomitant use of these agents may increase the hypotensive effects of enalapril. Concomitant use with nitroglycerine and other nitrates, or other vasodilators, may further reduce blood pressure.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE-inhibitors. Concomitant use of thiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with ACE-inhibitors. Use of enalapril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Tricyclic antidepressants/Antipsychotics /Anaesthetics/Narcotics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE-inhibitors may result in further reduction of blood pressure (see section 4.4).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 (COX-2) Inhibitors
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and others antihypertensive drugs. Therefore, the antihypertensive effect of angiotensin II receptor antagonists or ACE-inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

The co-administration of NSAIDs (including COX-2 inhibitors) and angiotensin II receptor antagonists or ACE-inhibitors exert an additive effect on the increase in serum potassium, and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function (such as the elderly or patients who are volume-depleted, including those on diuretic therapy). Therefore, the combination should be administered with caution in patients with compromised renal function. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy and periodically thereafter.

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.

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE-inhibitors.

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 sections 4.4 and 4.8).

Alcohol
Alcohol enhances the hypotensive effect of ACE-inhibitors.

Acetylsalicylic acid, thrombolytics and β-blockers
Enalapril can be safely administered concomitantly with acetyl salicylic acid (at cardiologic doses), thrombolytics and β-blockers.

Lercanidipine

Contraindications of concomitant use
Inhibitors of CYP3A4
Lercanidipine is known to be metabolised by the CYP3A4 enzyme and therefore inhibitors of CYP3A4 administered concurrently may interact with the metabolism and elimination of lercanidipine. 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).
Co-prescription of lercanidipine with inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir, erythromycin, troleandomycin, clarithromycin) should be avoided (see section 4.3).

Ciclosporin
Increased plasma levels of both lercanidipine and ciclosporin have been observed following concomitant administration. A study in young healthy volunteers has shown that when ciclosporin was administered 3 hours after the lercanidipine intake, the plasma levels of lercanidipine did not change, while the AUC of ciclosporin increased by 27%. However, the co-administration of lercanidipine with ciclosporin has caused a 3-fold increase of the plasma levels of lercanidipine and a 21% increase of the ciclosporin AUC.
Ciclosporin and lercanidipine should not be administered together (see section 4.3).

Grapefruit or grapefruit juice
As for other dihydropyridines, lercanidipine is sensitive to inhibition of metabolism by grapefruit or grapefruit juice, with a consequent rise in its systemic availability and increased hypotensive effect. Lercanidipine should not be taken with grapefruit or grapefruit juice (see section 4.3).

Concomitant use not recommended

Inducers of CYP3A4

Co-administration of lercanidipine with CYP3A4 inducers like anticonvulsants (e.g. phenytoin, phenobarbital, carbamazepine) and rifampicin should be approached with caution since the antihypertensive effect may be reduced and blood pressure should be monitored more frequently than usual (see section 4.4).

Alcohol

Alcohol should be avoided since it may potentiate the effect of vasodilating antihypertensive drugs (see section 4.4).

Precautions including dose adjustment

Substrates of CYP3A4

Caution should be exercised when lercanidipine is co-prescribed with other substrates of CYP3A4 like terfenadine, astemizole, class III antiarrhythmic drugs, such as amiodarone, quinidine, sotalol.

Midazolam

When concomitantly administered at a dose of 20 mg with midazolam p.o. to elderly volunteers, lercanidipine absorption was increased (by approximately 40%) and the rate of absorption was decreased (t_{max} was delayed from 1.75 to 3 hours). Midazolam concentrations were not modified.

Metoprolol

When lercanidipine was co-administered with metoprolol, a β-blocker eliminated mainly by the liver, the bioavailability of metoprolol was not changed while that of lercanidipine was reduced by 50%. This effect may be due to the reduction in hepatic blood flow caused by β-blockers and may therefore occur with other drugs of this class. Consequently, lercanidipine may be safely administered with β-adrenoceptor blocking drugs, but dose adjustment may be required.

Digoxin

Co-administration of 20 mg lercanidipine in patients chronically treated with β-methyldigoxin showed no evidence of pharmacokinetic interaction. However, a mean increase of 33% in digoxin C_{max} was observed, while AUC and renal clearance were not significantly modified. Patients on concomitant digoxin treatment should be closely monitored clinically 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 800 mg daily does not cause significant modifications in plasma levels of lercanidipine, but at higher doses caution is required since the bioavailability and the hypotensive effect of lercanidipine may be increased.

Simvastatin

When a 20 mg dose of lercanidipine was repeatedly co-administered with 40 mg of simvastatin, the AUC of lercanidipine was not significantly modified, while simvastatin AUC increased by 56% and that of its active metabolite, β-hydroxyacid by 28%. It is unlikely that such changes are of clinical relevance. No interaction is expected when lercanidipine is administered in the morning and simvastatin in the evening, as indicated for such a drug.

Warfarin
The co-administration of 20 mg lercanidipine to healthy volunteers given fasted 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 effects may be observed when lercanidipine is administered with other medications affecting blood pressure, such as alphablockers for the treatment of urinary symptoms, tricyclic antidepressants, neuroleptics. On the contrary, a reduction of the hypotensive effect may be observed with a concomitant use with corticosteroids.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

For enalapril
The use of ACE-inhibitors (enalapril) is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE-inhibitors (enalapril) is contra-indicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).
Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE-inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE-inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE-inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.
Exposure to ACE-inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). Maternal oligohydramnios, presumably representing decreased foetal renal function, has occurred and may result in limb contractures, craniofacial deformations and hypoplastic lung development. Should exposure to ACE-inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE-inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

For lercanidipine

There are no data from the use of lercanidipine in pregnant women. Studies in animals have not shown teratogenic effects (see section 5.3), but these have been observed with other dihydropyridine compounds.
Lercanidipine is not recommended during pregnancy and in women of childbearing-potential not using contraception (see section 4.4).

For enalapril and lercanidipine in association
There are no or limited amount of data from the use of enalapril maleate/lercanidipine HCl in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
Zaneril should not be used in the second and third trimester of pregnancy. It is not recommended in the first trimester of pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

For enalapril
Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of enalapril in breast-feeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In the case of an older infant, the use of enalapril in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

For lercanidipine
It is unknown whether lercanidipine/metabolite are excreted in human milk. A risk to the newborns/infants cannot be excluded. Lercanidipine should not be used during breast-feeding.

For enalapril and lercanidipine in association
Consequently, Zaneril should not be used during breast-feeding.

Fertility

No clinical data are available with lercanidipine. 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.

4.7 Effects on ability to drive and use machines

Zaneril has minor influence on the ability to drive and use machines. However, caution should be exercised because dizziness, asthenia, fatigue and rarely somnolence may occur (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety of Zaneril has been evaluated in five double-blind controlled clinical studies and in two long term open-label extension phases. In total, 1,141 patients have received Zaneril at a dose of 10 mg/10 mg, 20 mg/10 mg and 20 mg/20 mg. The undesirable effects observed with combination therapy have been similar to those already observed with one or the other of the constituents given alone. The most commonly reported adverse reactions during treatment with Zaneril were cough (4.03%), dizziness (1.67%) and headache (1.67%).

Tabulated summary of adverse reactions

In the table below, adverse reactions reported in clinical studies with Zaneril 10 mg/10 mg, 20 mg/10 mg and 20 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	
Rare:	Hypersensitivity
Metabolism and nutrition disorders	
Uncommon:	Hyperkalaemia
Psychiatric disorders	
Uncommon:	Anxiety
Nervous system disorders	
Common:	Dizziness, headache
Uncommon:	Dizziness postural
Ear and labyrinth disorders	
Uncommon:	Vertigo
Rare:	Tinnitus
Cardiac Disorders	
Uncommon:	Tachycardia, palpitations
Vascular disorders	
Uncommon:	Flushing, hypotension
Rare:	Circulatory collapse
Respiratory, thoracic and mediastinal disorders	
Common:	Cough
Rare:	Dry throat, oropharingeal pain
Gastrointestinal disorders	
Uncommon:	Abdominal pain, constipation, nausea
Rare:	Dyspepsia, lip oedema, tongue disorder, diarrhoea, dry mouth, gingivitis
Hepatobiliary Disorders	
Uncommon:	ALT increased, AST increased
Skin and sub-cutaneous tissue disorders	
Uncommon:	Erythema
Rare:	Angioedema, swelling face, dermatitis, rash, urticaria
Musculoskeletal, connective tissue disorders	
Uncommon:	Arthralgia
Renal and urinary disorders	
Uncommon:	Pollakiuria
Rare:	Nocturia, polyuria
Reproductive System and Breast Disorders	
Rare:	Erectile dysfunction
General disorders and administration site conditions	

Uncommon:	Asthenia, fatigue, feeling hot, oedema peripheral

Undesirable effects occurring in one patient only are reported under the frequency rare.

Additional information on the individual components

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

Enalapril alone
Among the adverse drug reactions reported for enalapril are:

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)

Psychiatric disorders:
Common: depression
Uncommon: confusion, nervousness, insomnia
Rare: dream abnormality, sleep disorders

Nervous system disorders:
Very common: dizziness
Common: headache, syncope, taste alteration
Uncommon: somnolence, paraesthesia, vertigo

Eye disorders:
Very common: blurred vision

Ear and labyrinth disorders:
Uncommon: tinnitus

Cardiac disorders:
Common: chest pain, rhythm disturbances, angina pectoris, tachycardia
Uncommon: palpitations, myocardial infarction or cerebrovascular accident*, possibly secondary to excessive hypotension in high risk patients (see section 4.4)
* Incidence rates were comparable to those in the placebo and active control groups in the clinical trials.

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 4.4)
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 leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

Musculoskeletal, connective tissue, 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: malaise, fever

Investigations:
Common: hyperkalaemia, increases in serum creatinine
Uncommon: increases in blood urea, hyponatremia
Rare: elevation of liver enzymes, elevation of serum bilirubin.

Lercanidipine alone

The adverse drug reactions most commonly reported in clinical trials and in the post-marketing experience are peripheral oedema, headache, flushing, tachycardia and palpitations.

Immune system disorders:
Rare: hypersensitivity

Nervous system disorders:
Common: headache
Uncommon: dizziness
Rare: somnolence, syncope

Cardiac disorders:
Common: tachycardia, palpitations
Rare: angina pectoris

Vascular disorders:
Common: flushing
Uncommon: hypotension

Gastrointestinal disorders:
Uncommon: nausea, dyspepsia, abdominal pain upper
Rare: vomiting, diarrhoea
Not known: gingival hypertrophy[1], peritoneal cloudy effluent[1]

Hepatobiliary disorders:
Not known: serum transaminase increased[1]

Skin and subcutaneous tissue disorders:
Uncommon: rash, pruritus
Rare: urticaria
Not known: angioedema[1]

Musculoskeletal and connective tissue disorders:
Uncommon: myalgia

Renal and urinary disorders:
Uncommon: polyuria
Rare: pollakiuria

General disorders and administration site conditions:
Common: oedema peripheral
Uncommon: asthenia, fatigue
Rare: chest pain

[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 have any adverse effect on blood sugar or serum lipid levels.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 (blood pressure systolic decreased, bradycardia, restlessness, somnolence and flank pain) could also be due to the concomitant administration of high doses of other drugs (e.g. beta-blockers).

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.

As with other dihydropyridines, lercanidipine overdosage results in excessive peripheral vasodilation 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:
The recommended treatment of overdosage with enalapril is intravenous infusion of saline solution. If hypotension occurs, the patients 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 maleate should be taken (e.g. vomiting, gastric lavage, administration of absorbents or sodium sulfate). Enalaprilat can be removed from the circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be continuously monitored.

With lercanidipine, clinically significant hypotension requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output. In view of the prolonged pharmacological effect of lercanidipine, it is essential that the cardiovascular status of the patient is monitored for 24 hours at least. Since the product has a high protein binding, dialysis is not likely to be effective. Patients in whom a moderate to severe intoxication is anticipated should be observed in a high-care setting.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE-inhibitors and calcium channel blockers: enalapril and lercanidipine.

ATC code: C09BB02

Zaneril is the fixed combination of an ACE-inhibitor (enalapril) and a calcium channel blocker (lercanidipine), two antihypertensive compounds with complementary mechanism of action to control blood pressure in patients with essential hypertension.

Enalapril

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 vasopressor agent angiotensin II. After absorption, enalapril is hydrolysed to enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to the removal of negative feedback of renin release) and decreased aldosterone secretion.

Since ACE is identical to kininase II, enalapril may also inhibit the degradation of bradykinin, a potent vasodepressor peptide. However the role of this mechanism in the therapeutic effects of enalapril is still not understood.

Although the mechanism by which enalapril reduces blood pressure is primarily attributed to suppression of the renin-angiotensin-aldosterone system, enalapril is antihypertensive even in patients with low renin levels.

Administration of enalapril to hypertensive patients reduces 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 normally occurs 2 to 4 hours after oral administration of a single dose of enalapril. Onset of the antihypertensive action was usually seen after one hour with maximum reduction of blood pressure observed 4 to 6 hours after administration. The duration of action is dose-related, but with recommended doses, antihypertensive and haemodynamic effects have been shown to persist 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 pre-treatment 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.

Two large randomised, controlled trials ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Lercanidipine

Lercanidipine is a calcium antagonist of the dihydropyridine group and inhibits the transmembrane influx of calcium into cardiac and smooth muscle. The mechanism of the antihypertensive action is based on a direct relaxant effect on vascular smooth muscle, thus lowering total peripheral resistance. Despite its short pharmacokinetic plasma half-life, lercanidipine is endowed with a prolonged antihypertensive activity because of its high membrane partition coefficient, and is devoid of negative inotropic effects due to its high vascular selectivity.

Since the vasodilatation produced by lercanidipine has a gradual onset, acute hypotension with reflex tachycardia has only been rarely observed in hypertensive patients.

As with other asymmetric 1,4-dihydropyridines, the antihypertensive activity of lercanidipine is mainly due to its (S)-enantiomer.

Enalapril/Lercanidipine

The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

- Zaneril 10mg/10mg

In a pivotal phase III, double blind, add-on clinical trial conducted in 342 non responders to lercanidipine 10 mg (defined as SDBP 95-114 and SSBP 140-189 mmHg), the reduction in trough SSBP was 5.4 mmHg greater with the combination enalapril 10 mg/lercanidipine 10 mg than with lercanidipine 10 mg alone after 12 weeks of double-blind treatment (-7.7 mmHg vs -2.3 mmHg, p<0.001). Also the reduction in trough SDBP was 2.8 mmHg greater with the combination as compared to the monotherapy (-7.1 mmHg vs -4.3 mmHg, p<0.001). Responder rates resulted significantly higher with combination therapy than with monotherapy: 41% vs 24% (p< 0.001) for SSBP and 35% vs 24% (p=0.032) for SDBP. A significantly higher percentage of patients on combination treatment experienced normalisation of SSBP (39% vs 22%, p<0.001) and of SDBP (29% vs 19%, p=0.023) compared with patients on monotherapy. In the open-label long term follow-up phase of this study a titration to the combination enalapril 20 mg/lercanidipine 10 mg was allowed if BP remained >140/90 mmHg: titration occurred in 133/221 patients and SDBP normalised after titration in 1/3 of these cases.

- Zaneril 20mg/10mg

In a pivotal phase III, double blind, add-on clinical trial conducted in 327 non responders to enalapril 20 mg (defined as SDBP 95-114 and SSBP 140-189 mmHg), patients on enalapril 20 mg/lercanidipine 10 mg achieved a significantly greater reduction in trough SSBP compared with those on monotherapy (-9.8 vs -6.7 mmHg, p=0.013) and in trough SDBP (-9.2 vs -7.5 mmHg, p=0.015). Responder rates were not significantly higher with combination therapy than with monotherapy (53% vs 43%, p=0.076 for SDBP and 41% vs 33%, p=0.116 for SSBP) and a not significantly higher percentage of patients on combination therapy experienced normalisation of SDBP (48% vs. 37%, p=0.055) and of SSBP (33% vs 28%, p=0.325) compared with patients on monotherapy.

- Zaneril 20mg/20mg

In a placebo and active-controlled randomised double blind study with a factorial design conducted on 1,039 patients with moderate hypertension (defined as office SDBP 100-109 mmHg, SSBP < 180 mmHg and home DBP ≥ 85 mmHg), patients on enalapril 20mg/lercanidipine 20 mg had a significantly greater reductions in office and home SDBP and SSBP compared with placebo (P<0.001). Clinically relevant differences in the change from baseline in office SDBP at trough were observed between combination therapy 20mg/20mg (–15.2 mmHg, n=113) in comparison with enalapril 20mg (–11.3 mmHg, P=0.004, n=113) or lercanidipine 20mg alone (–13.0 mmHg, P=0.092, n=113). Similarly, clinically relevant differences were observed in the change from baseline in office SSBP at trough between combination therapy 20mg/20mg (–19.2 mmHg) compared with lercanidipine 20mg (–13.0 mmHg, P=0.002) or enalapril 20mg alone (–15.3 mmHg, P=0.055). Clinically relevant differences were also observed in home SBP and DBP. A significant increase in the responder rates for SDBP (75%) and SSBP (71%) was observed with combination therapy 20mg/20mg over placebo (P<0.001) and both monotherapies (P<0.01). Normalisation of blood pressure was achieved by a higher percentage of patients treated with combination therapy 20mg/20mg (42%) than with placebo (22%).

5.2 Pharmacokinetic properties

No pharmacokinetic interactions have been observed on concurrent administration of enalapril and lercanidipine.

Pharmacokinetics of enalapril

Absorption

Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril maleate is approximately 60%. The absorption of oral enalapril is not affected by the presence of food in the gastrointestinal tract.

Distribution

Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin-converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur about 4 hours after an oral dose of enalapril maleate. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril is 11 hours. In subjects with normal renal function, steady-state serum concentrations of enalaprilat was reached after four days of treatment.

Over the range of concentrations which are therapeutically relevant, enalaprilat binding to human plasma proteins does not exceed 60%.

Biotransformation

Apart from the conversion to enalaprilat, there is no evidence for significant metabolism of enalapril.

Elimination

Excretion of enalaprilat is primarily renal. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and unchanged 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), the 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 ≤ 30 ml/min), the 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).

Enalaprilate may be removed from the general circulation by haemodialysis. The dialysis clearance is 62 ml/min.

Lactation

After a single 20 mg oral dose in five postpartum women, the average peak enalapril milk level was 1.7µg/L (range 0.54 to 5.9 µg/L) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1.7µg/L (range 1.2 to 2.3µg/L); peaks occurred at various times over the 24-hour period. Using the peak milk level data, the estimated maximum intake of an exclusively breastfed infant would be about 0.16% of the maternal weight-adjusted dosage. A woman who had been taking oral enalapril 10 mg daily for 11 months had peak enalapril milk levels of 2 µg/L 4 hours after a dose and peak enalaprilat levels of 0.75 µg/L about 9 hours after the dose. The total amount of enalapril and enalaprilat measured in milk during the 24 hour period was 1.44µg/L and 0.63 µg/L of milk respectively. Enalaprilat milk levels were undetectable

(<0.2µg/L) 4 hours after a single dose of enalapril 5 mg in one mother and 10mg in two mothers; enalapril levels were not determined.

Pharmacokinetics of lercanidipine

Absorption

Lercanidipine is completely absorbed after oral administration and peak plasma levels are reached after approximately 1.5 - 3 hours.

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

Due to the high first-pass metabolism, the absolute bioavailability of oral lercanidipine in non-fasted conditions is about 10% However, the bioavailability on ingestion by healthy volunteers under fasting conditions is reduced to 1/3.

Oral availability of lercanidipine increases 4-fold when it is ingested up to 2 hours after a high-fat meal. Hence the drug should be taken before meals.

Distribution

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

The degree of plasma 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 higher.

Biotransformation

Lercanidipine is extensively metabolised by CYP3A4; no parent substance is found either in urine or faeces. It is predominantly converted into inactive metabolites and approximately 50% of the dose is excreted in the urine.

In vitro experiments with human liver microsomes have demonstrated that lercanidipine shows slight inhibition of the two enzymes CYP3A4 and CYP2D6 at concentrations 160- and 40-times higher than the peak plasma levels achieved after administration of the 20 mg dose.

Furthermore, interaction studies in humans have shown that lercanidipine does not modify the plasma levels of midazolam, a typical substrate of CYP3A4, or of metoprolol, a typical substrate of CYP2D6. Therefore, at therapeutic doses, lercanidipine is not expected to inhibit the biotransformation of drugs metabolised by CYP3A4 or CYP2D6.

Elimination

Elimination essentially occurs through biotransformation.

A mean terminal elimination half-life of 8-10 hours was calculated, and due to the high binding to lipid membranes, therapeutic activity lasts for 24 hours. No accumulation was shown after repeated administration.

Linearity/non-linearity

Oral administration of lercanidipine results in plasma levels that are not directly proportional to the dose (non-linear kinetics). After 10, 20 or 40 mg, peak plasma concentrations were in the ratio of 1:3:8 and areas under the plasma concentration-

time curves in the ratio of 1:4:18, suggesting a progressive saturation of first pass metabolism. Accordingly, availability increases with dosage elevation.

Special populations
It has been shown that the pharmacokinetic behaviour of lercanidipine in elderly patients and in patients with mild to moderate renal dysfunction or mild to moderate hepatic impairment is similar to that observed in the general patient population. Patients with severe renal dysfunction or dialysis-dependent patients showed higher concentrations of the drug (approximately 70%). In patients with moderate to severe hepatic impairment, systemic bioavailability of lercanidipine is probably increased because the drug is normally extensively metabolised in the liver.

5.3 Preclinical safety data

Enalapril/lercanidipine combination
Potential toxicity of the fixed combination of enalapril and lercanidipine was studied in rats after oral administration up to 3 months and in two genotoxicity tests. The combination did not alter the toxicological profile of the two individual components.

The following data exist for the two individual components, enalapril and lercanidipine.

Enalapril
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
Reproductive toxicity studies suggest that enalapril has no effects on fertility and reproductive performance in rats, and is not teratogenic. In a study in which female rats were dosed prior to mating through gestation, an increased incidence of rat pup deaths occurred during lactation. The compound has been shown to cross the placenta and is excreted in milk. Angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on the late foetal development, resulting in foetal death and congenital effects, in particular affecting the skull. Foetotoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported. These developmental anomalies are thought to be partly due to a direct action of ACE-inhibitors on the foetal renin angiotensin system and partly due to ischaemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrients delivery to the foetus.

Lercanidipine
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.
The relevant effects which have been observed in long term studies in rats and dogs were related, directly or indirectly, to the known effects of high doses of Ca-antagonist, predominantly reflecting exaggerated pharmacodynamic activity.
Treatment with lercanidipine had no effect on fertility or general reproductive performance in rats, but at high doses induced pre- and post- implantation losses and delay in foetal development. There was no evidence of any teratogenicity effect in rats and rabbits, but other dihydropyridines have been found to be teratogenic in animals. Lercanidipine induced dystocia when administered at high dose (12 mg/kg/day) during labour.

The distribution of lercanidipine and/or its metabolites in pregnant animals and their excretion in breast milk have not been investigated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate
Cellulose microcrystalline
Sodium starch glycolate type A
Povidone K30
Sodium hydrogen carbonate
Magnesium stearate

Film-Coating:
Hypromellose 5 cP
Titanium dioxide (E171)
Talc
Macrogol 6000
Quinoline yellow aluminium Lake (E104)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture. Do not store above 25°C.

6.5 Nature and contents of container

Polyamide-aluminium-PVC/aluminium blister
Packs of 7, 14, 28, 30, 35, 42, 50, 56, 90, 98 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Recordati Pharmaceuticals Limited,
Breakspear Park, Breakspear Way,
Hemel Hempstead,
HP 4TZ,
United Kingdom

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