VASODIP COMBO

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vasodip Combo 10, tablets
Vasodip Combo 20, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vasodip Combo 10:
Each tablet contains 10 mg lercanidipine hydrochloride (equivalent to 9.44 mg lercanidipine) and 10 mg enalapril maleate (equivalent to 7.64 mg enalapril).

Vasodip Combo 20:
Each tablet contains 10 mg lercanidipine hydrochloride (equivalent to 9.44 mg lercanidipine) and 20 mg enalapril maleate (equivalent to 15.29 mg enalapril).

Excipients:
Vasodip Combo 10: one tablet contains approximately 97 mg of lactose.
Vasodip Combo 20: one tablet contains approximately 87 mg of lactose.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vasodip Combo 10:
White, biconvex, round film-coated tablets.
Vasodip Combo 20:
Yellow, biconvex, round film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vasodip Combo 10: Treatment of essential hypertension in patients whose blood pressure is not adequately controlled by lercanidipine monotherapy.

Vasodip Combo 20: Treatment of essential hypertension in patients whose blood pressure is not adequately controlled by enalapril monotherapy.

4.2 Posology and method of administration

Fixed combination Vasodip Combo should not be used for initial treatment of hypertension

The combination Vasodip Combo 10 can be given to patients whose blood pressure cannot be controlled adequately by treatment with 10 mg lercanidipine alone.

The combination of Vasodip Combo 20 can be given to patients whose blood pressure cannot be controlled adequately by treatment with 20 mg enalapril alone.
Individual dose titration with the components can be recommended. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

The recommended dose is 1 tablet taken once daily at least 15 minutes before a meal.
Treatment should be preferably administered in the morning. This product should not be administered with grapefruit juice (see section 4.3 and 4.5).

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

Children and adolescents under 18 years of age: Since there is no clinical experience in patients under 18 years of age, use in children and adolescents is not currently recommended.

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

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

4.3 Contraindications

Vasodip Combo must not be taken in:

- Hypersensitivity to a therapeutically active constituent (enalapril or lercanidipine), to any ACE-inhibitor or dihydropyridine calcium channel blocker or to any other constituent of this medicinal product.
- History of angioedema associated with ACE-inhibitor therapy
- Hereditary or idiopathic angioedema.
- Association with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR<60ml/min/1.73m^2) (see section 4.5 and 5.1)
- second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- left ventricular outflow obstruction, including aortic stenosis
- untreated congestive heart failure
- unstable angina pectoris
- within 1 month of a myocardial infarction
- severe renal impairment (creatinine clearance < 30 ml/min), including patients undergoing haemodialysis
- severe hepatic impairment
- co-administration with:
    - strong CYP 3A4 inhibitors (see section 4.5)
    - ciclosporin (see section 4.5)
    - grapefruit juice (see section 4.5)

4.4 Special warnings and special precautions for use

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 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
Particular caution is recommended in the use of lercanidipine in patients with sick-sinus syndrome (without a pacemaker).

Left ventricular dysfunction and ischaemic heart disease
Although haemodynamic controlled studies revealed no impairment of ventricular function, caution must be exercised when treating patients with left ventricular dysfunction with calcium channel blockers. It has been suggested that patients with ischaemic heart disease show an elevated cardiovascular risk under treatment with some short-acting dihydropyridines. Although lercanidipine is long-acting, caution is advised in these patients.
In rare cases, some dihydropyridines can cause 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 4.8).

Use in 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 under enalapril treatment is part of the normal medical care of these patients.
Reports of renal failure associated with the use of enalapril have been made especially in patients with severe heart failure or underlying renal disease, including renal artery stenosis.
If diagnosed promptly and treated appropriately, renal failure under 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

Patients with bilateral renal artery stenosis or stenosis of the artery of a single functioning kidney are particularly at risk of developing hypotension or renal insufficiency under ACE-inhibitor therapy. 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 renal function.

Kidney transplantation
There is no experience in the use of lercanidipine or enalapril in patients who have recently undergone renal transplantation. Therefore treatment of these patients with Vasodip Combo is 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.

Neutropenia/agranulocytosis
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients on ACE-inhibitors. Neutropenia is rare in patients with normal renal function and without particular risk factors. Enalapril should be used with extreme caution in patients with collagen vascular disease, those under treatment with immunosuppressants, allopurinol, procainamide or if several of these risk factors are present, especially in pre-existing impairment of renal function. Severe infections occurred in some of these patients that in few cases did not respond to intensive antibiotic treatment. If enalapril is used in such patients, regular monitoring of leucocytes is advised and patients should be instructed to report any signs of infection to their doctor.

Hypersensitivity/angioneurotic oedema

Angioneurotic oedema with involvement of the face, extremities, lips, tongue, glottis and/or larynx, has been reported in patients treated with ACE-inhibitors, including enalapril. It may occur at any time during treatment. In such cases, enalapril must be stopped immediately. The patient is to be carefully monitored in order to ensure that the symptoms have fully resolved before discharge from the hospital.

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.
When the tongue, glottis or larynx are affected and are likely to cause airway obstruction, appropriate treatment must be instituted promptly (e.g. subcutaneous administration of adrenalin 1:1000 (0.3 ml to 0.5 ml) and/or measures to ensure a patent airway.

A higher incidence of angioedema on ACE-inhibitors has been reported in black patients, when compared to non-black patients.

Patients with a history of angioedema not triggered by an ACE-inhibitor can be at a higher risk of developing angioedema if they are to receive an ACE-inhibitor (see also 4.3).

Anaphylactoid reactions during desensitisation with insect venoms
Life-threatening anaphylactoid reactions have occurred rarely during desensitisation therapy against insect venoms and concurrent use of an ACE-inhibitor. These reactions can be avoided by temporarily discontinuing the ACE-inhibitor prior to each desensitisation.

Anaphylactoid reactions during LDL apheresis
Life-threatening anaphylactoid reactions have occurred rarely during a low density lipoprotein (LDL)-apheresis with dextran sulfate and concurrent use of an ACE-inhibitor. These reactions can be avoided by temporarily discontinuing the ACE-inhibitor prior to each apheresis.

Hypoglycemia
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 in connection with the use of ACE-inhibitors. Typically, the cough is non-productive, persistent and subsides after discontinuation of the therapy. A cough induced by ACE-inhibitor should also be considered in the differential diagnosis of cough.

Surgery/anaesthesia
In patients undergoing major surgery or anaesthesia with agents that reduce blood pressure, enalapril inhibits the formation of angiotensin II, that would otherwise occur due to a compensatory secretion of renin. If hypotension develops as a result of this mechanism, it can be corrected by volume expansion.

Hyperkalaemia

An increase in serum potassium has been observed in some patients on ACE-inhibitors including enalapril. Risk factors for hyperkalaemia are: renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes as well as concurrent treatment with other drugs that can lead to an increase in serum potassium values (e.g. heparin). 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 (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
CYP3A4 inducers such as anticonvulsants (e.g. phenytoin, carbamazepine) and rifampicin can reduce serum levels of lercanidipine so that the efficacy of the drug can be lower 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
Vasodip Combo 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 planning to become pregnant (see section 4.6)

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

Pediatric use
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 vasodilator antihypertensives (see section 4.5).

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Vasodip Combo.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Lercanidipine
Contraindicated combinations
Inhibitors of CYP3A4
Since lercanidipine is metabolised by the enzyme CYP3A4, simultaneously administered inhibitors and inducers of CYP3A4 may interact with the metabolism and excretion of lercanidipine.
The combination of lercanidipine and strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir, erythromycin, troleandomycin) is contraindicated (see section 4.3).
An interaction study with ketoconazole, a strong inhibitor of CYP3A4, showed a marked rise in plasma levels of lercanidipine (a 15-fold increase in area under the drug concentration-time curve [AUC] and an 8-fold increase in C_{max} of the eutomer S-lercanidipine).

Ciclosporin
Ciclosporin and lercanidipine must not be used together (see section 4.3).
Increased plasma concentrations of both drugs have been observed following concurrent administration. A study in healthy young volunteers showed no changes in plasma lercanidipine levels

when ciclosporin was taken 3 hours after ingestion of lercanidipine, but the AUC of ciclosporin rose by 27%. Co-medication of lercanidipine with ciclosporin caused a 3-fold rise in plasma lercanidipine levels and a 21% increase in AUC of ciclosporin.

Grapefruit juice
Lercanidipine should not be taken with grapefruit juice (see section 4.3).
As with other dihydropyridines, the metabolism of lercanidipine can be inhibited by the ingestion of grapefruit juice, resulting in a rise in the systemic availability of lercanidipine and increased hypotensive effect.

Combinations requiring precautions for use
Alcohol
Alcohol should be avoided since it may potentiate the effect of vasodilator antihypertensives (see section 4.4).

Substrates of CYP3A4
Caution is required on the co-prescribing of lercanidipine with other substrates of CYP3A4 such as terfenadine, astemizole, Class III antiarrhythmics, e.g. amiodarone, quinidine.

Inducers of CYP3A4
Concurrent use of lercanidipine with CYP3A4 inducers such as anticonvulsants (e.g. phenytoin, carbamazepine) and rifampicin should be approached with caution, because the antihypertensive effect of lercanidipine can be reduced. Blood pressure must therefore be monitored more frequently than usual.

Digoxin
Co-administration of 20 mg lercanidipine in patients chronically treated with ß-methyldigoxin showed no evidence of pharmacokinetic interaction. Healthy volunteers treated with digoxin after administration of 20 mg lercanidipine showed a mean increase in digoxin C_{max} of 33%, whereas neither AUC nor renal clearance were significantly altered. Patients on concomitant treatment with digoxin should be closely monitored for clinical signs of digoxin toxicity.

Combinations to be taken into account
Midazolam
In elderly volunteers the concurrent administration of oral midazolam 20 mg enhanced the absorption of lercanidipine (by about 40%) and decreased its rate of absorption (t_{max} was delayed from 1.75 to 3 hours). No changes in midazolam concentrations occurred.

Metoprolol
When lercanidipine was co-administered with metoprolol - a ß-blocker predominantly eliminated by the liver - the bioavailability of metoprolol was unchanged, whereas the bioavailability of lercanidipine was reduced by 50%. This effect may be due to the reduction in hepatic blood flow caused by ß-blockers and hence might also occur with other preparations of this class of drug. Nevertheless, lercanidipine can be safely used at the same time as blockers of β-adrenergic receptors.

Cimetidine
Concomitant administration of cimetidine 800 mg daily does not cause significant modifications in plasma levels of lercanidipine, but caution is required at higher doses since the bioavailability of lercanidipine, and therefore its hypotensive effect may be increased.

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

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, whereas the AUC of simvastatin increased by 56% and that of its principal active metabolite, ß-hydroxyacid by 28%. It is unlikely that such changes are of clinical relevance. No interaction is expected if lercanidipine is administered in the morning and simvastatin in the evening, as indicated for such a drug.

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

Pediatric population

Interaction studies have only been performed in adults.

Enalapril maleate

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 and 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).

Lithium
Reversible increases in serum lithium concentrations and toxic effects have been reported during concomitant administration of lithium with ACE-inhibitors. Concomitant use of thiazide diuretics may increase serum lithium concentrations and hence enhance the risk of lithium toxicity with ACE-inhibitors. Use of enalapril with lithium is therefore not recommended, but if the combination is necessary, serum lithium levels must be carefully monitored (see section 4.4).

Antidiabetics
Epidemiological studies have suggested that concomitant administration of ACE-inhibitors and antidiabetic drugs (insulin, oral antidiabetics) may cause an increased blood glucose-lowering effect, with risk of hypoglycaemia. These cases are apparently more likely to occur in the first weeks of combined treatment and in patients with renal impairment (see sections 4.4 and 4.8).

Diuretics (thiazide 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 giving salt, or by initiating therapy with a low dose of enalapril.

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.

Alcohol
Alcohol enhances the hypotensive effect with ACE inhibitors.

Tricyclic antidepressants/neuroleptics/anaesthetics/narcotics
Concomitant use of certain anaesthetic agents, tricyclic antidepressants and neuroleptics with ACE-inhibitors may lead to a further reduction in blood pressure (see section 4.4).

Other antihypertensives
Concomitant use of other antihypertensives may increase the hypotensive effects of enalapril. Concomitant use of nitroglycerine and other nitrates or other vasodilators may further reduce blood pressure.

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects 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.

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.

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 fetal 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
Animal studies with lercanidipine have not shown teratogenic effects, but these have been observed with other dihydropyridine compounds.

No clinical data on exposed pregnancies are available for lercanidipine, Therefore its use is not recommended during pregnancy or in women with childbearing potential unless effective contraception is used.

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).

Vasodip Combo 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.

Lactation
For enalapril
Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see 5.2). Although these concentrations seem to be clinically irrelevant, the use of Vasodip Combo in breastfeeding 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 Vasodip Combo 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
The excretion of lercanidipine in human milk is unknown.

For enalapril and lercanidipine in association
Consequently, the use of Vasodip Combo is not recommended during lactation.

Fertility
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

Vasodip Combo has minor influence on the ability to drive and use machines. However, caution is advised because dizziness, asthenia, fatigue and in rare cases somnolence may occur (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety of Vasodip Combo 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 Vasodip Combo 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 Vasodip Combo 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 Vasodip Combo 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

Lercanidipine alone
The adverse drug reactions most commonly reported in controlled clinical trials were headache, dizziness, oedema peripheral, tachycardia, palpitations and flushing, with each occurring in less than 1% of patients.

Immune system disorders
Very rare: hypersensitivity

Psychiatric disorders
Rare: somnolence

Nervous system disorders
Uncommon: headache, dizziness

Cardiac disorders
Uncommon: tachycardia, palpitations
Rare: angina pectoris

Vascular disorders
Uncommon: flushing
Very rare: syncope

Gastrointestinal disorders
Rare: nausea, dyspepsia, diarrhoea, abdominal pain, vomiting

Skin and subcutaneous tissue disorders
Rare: rash

Musculoskeletal and connective tissue disorders
Rare: myalgia

Renal and urinary disorders
Rare: polyuria

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

From spontaneous reports in post-marketing experience, the following adverse reactions have been reported very rarely (<1/10000): gingival hypertrophy, reversible increases in serum levels of hepatic transaminases, hypotension, urinary frequency and chest pain.
Some dihydropyridines may rarely lead to precordial localised 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 occur.
Lercanidipine does not appear to have any adverse effect on blood sugar or serum lipid levels.

<u>*Enalapril alone*</u>
Among the adverse drug reactions reported for enalapril are:

Blood and lymphatic system disorders:
Uncommon: anaemia (including aplastic and haemolytic forms)
Rare: neutropenia, decreases in hemoglobin, decreases in hematocrit , thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, lymphadenopathy, autoimmune disorder.

Endocrine disorders:
Not known: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Metabolism and nutrition disorders:
Uncommon: hypoglycaemia (see 4.4)

Nervous system and psychiatric disorders:
Common: depression, headache
Uncommon: confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo
Rare: dream abnormality, sleep disorders

Eye disorders:
Very common: vision blurred

Cardiac and vascular disorders:
Very common: dizziness

Common: hypotension (including orthostatic hypotension), syncope, rhythm disturbances, angina pectoris, tachycardia, chest pain
Uncommon: palpitations, myocardial infarction or cerebrovascular accident*, possibly secondary to excessive hypotension in high-risk patients (see section 4.4)

Rare: Raynaud's phenomenon

* Incidence rates were comparable to those in the placebo and active control groups in the clinical trials.

Respiratory, thoracic and mediastinal disorders:
Very common: cough
Common: dyspnoea
Uncommon: rhinorrhoea, sore throat and hoarseness, bronchospasms/asthma
Rare: pulmonary infiltrates, rhinitis, allergic alveolitis /eosinophilic pneumonia

Gastrointestinal disorders:
Very common: nausea
Common: diarrhoea, abdominal pain, dysgeusia
Uncommon: ileus, pancreatitis, vomiting, dyspepsia, constipation, gastric irritations, dry mouth, peptic ulcer, anorexia.
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 edema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx have been reported (see section 4.4)

Uncommon: hyperhidrosis, pruritus, urticaria, alopecia
Rare: erythema multiforme, Stevens-Johnson syndrome, dermatitis exfoliative, toxic epidermal necrolysis, pemphigus, erythroderma.

A symptom complex has been reported which may include some or all of the following symptoms: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, positive antinuclear antibodies (ANA), elevated erythrocyte sedimentation rate (ESR), eosinophilia and leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

Renal and urinary disorders:
Uncommon: renal impairment, 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 malaise, tinnitus, flushing, fever

Investigations:
Common: blood potassium increased, blood creatinine increased
Uncommon: blood urea increased, blood sodium decreased
Rare: hepatic enzyme increased, blood bilirubin increased.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

4.9 Overdose

In the post-marketing experience, some cases of intentional overdose requiring hospitalization 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, overdose with lercanidipine might be expected to cause excessive peripheral vasodilatation with marked hypotension and reflex tachycardia.

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 should be continuously monitored.

With lercanidipine, in the case of severe hypotension, bradycardia and unconsciousness, cardiovascular support can be helpful, with intravenous atropine to counteract the bradycardia. In view of the prolonged pharmacological action of lercanidipine, the cardiovascular status of patients who have taken an overdose must be monitored for at least 24 hours. There is no information about the value of dialysis. Since the drug is highly lipophilic, it is very unlikely that plasma levels will be indicative of the duration of the risk phase. Dialysis may not be effective.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors and calcium channel blockers: enalapril and lercanidipine.
ATC code: C09BB02

Vasodip Combo 10 is a fixed combination of an ACE inhibitor (enalapril 10 mg) and a calcium channel blocker (lercanidipine 10 mg).
Vasodip Combo 20 is a fixed combination of an ACE inhibitor (enalapril 20 mg) and a calcium channel blocker (lercanidipine 10 mg

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. Due to its high membrane partition coefficient, lercanidipine has a prolonged antihypertensive action, and is devoid of negative ionotropic effects because of its high vascular selectivity.

Since the vasodilation 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

Enalapril maleate is the maleate salt of enalapril, a derivative of two aminoacids, – 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 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 antihypertensive even in patients with low renin level.

Administration of enalapril to hypertensive patients reduces both supine and standing blood pressure, without a significant increase in heart rate.

Symptomatic postural hypotension is rare. In some patients it may take a few weeks of treatment before optim blood pressure control is achieved. Abrupt withdrawal of enalapril is not associated with a rapid increase in blood pressure.

Effective inhibition of ACE activity normally occurs 2-4 hours after oral administration of a single dose of enalapril. Onset of the antihypertensive action was usually seen after 1 hour with maximum reduction of blood pressure observed 4-6 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.

Haemodynamic studies in patients with essential hypertension showed that the blood pressure reduction was associated with a decrease in peripheral arterial resistance and an increase in cardiac output; there was little or no change in heart rate. Following administration of enalapril, renal blood flow increased whilst glomerular filtration rate remained unchanged. There were no signs of sodium or water retention. However, in patients with low glomerular filtration rate prior to treatment, this rate was 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.

Enalapril/Lercanidipine

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

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 normalization 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 normalized after titration in 1/3 of these cases.

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 normalization of SDBP (48% vs. 37%, $p=0.055$) and of SSBP (33% vs 28%, $p=0.325$) compared with patients on monotherapy

In a placebo and active-controlled randomized 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 $\geq$ 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). Normalization 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 were observed on concurrent administration of enalapril and lercanidipine.

Pharmacokinetics of lercanidipine

Absorption

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

Additional information on 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.

Pharmacokinetics of enalapril
Absorbtion
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, enalapril 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 enalaprilate, 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 dialisys 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.

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 for 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.

Lercanidipine
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.

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.

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 fetal 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.

Enalapril
Preclinical 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 effect 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. ACE-inhibitors, as a class, have been shown to induce adverse effects on the late fetal development, resulting in fetal death and congenital effects, in particular affecting the skull. Fetotoxicity, 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 fetal renin angiotensin system and partly due to ischemia resulting from maternal hypotension and decreases in fetal-placental blood flow and oxygen/nutrients delivery to the fetus.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Vasodip Combo 10 and Vasodip Combo 20:
Tablet core
Lactose monohydrate, Cellulose microcrystalline, Sodium starch glycolate (type A), Povidone, Sodium hydrogen carbonate, Magnesium stearate.

Vasodip Combo 10:
Film-coating
Hypromellose, Titanium dioxide (E171), Talc, Macrogol 6000

Vasodip Combo 20:
Film-coating
Hypromellose, Titanium dioxide (E171), Talc, Macrogol 6000, Quinoline Yellow aluminium lake (E104), Iron oxide yellow (E172).

6.2 Incompatibilities

None known.

6.3 Special precautions for storage

Store in the original container and at temperature below 25^0C

6.4 Instructions for use and handling and disposal

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

7. MARKETING AUTHORISATION HOLDER

Dexcel LTD
1 Dexcel st., Or-Akiva 3060000.

8. MARKETING AUTHORISATION NUMBER(S)

Vasodip Combo 10: 141 06 31726 00

Vasodip Combo 20: 141 05 31727 00

9. Prescription status

Prescription only

The format of this leaflet was determined by the ministry of health (MOH) and its content was checked and approved by the MOH on 10/2015.