SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ENEAS 10 mg/20 mg tablets
Enalapril maleate/Nitrendipine 10 mg/20 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

10 mg Enalapril maleate
20 mg Nitrendipine

Excipient(s) with known effect:
Each tablet of Eneas 10 mg/20 mg tablets contains 63.58 mg of lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet.
The tablets are yellow, oblong and biconvex with the engraving "E/N" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential arterial hypertension in patients whose blood pressure is not adequately controlled on enalapril or nitrendipine alone.
See sections 4.3, 4.4, 4.5 and 5.1.

4.2 Posology and method of administration

Individual dose titration with the components can be recommended.
When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.

Adults, including the elderly:
The recommended posology is one tablet a day.

Patients with hepatic impairment:
ENEAS is contraindicated in patients with severe hepatic impairment (see 4.3). In patients with mild to moderate hepatic impairment neither enalapril nor nitrendipine in monotherapy are contraindicated, but there is no experience regarding the administration of ENEAS in these cases. Therefore ENEAS should be given with caution if indicated to these patients (see 4.4).

Patients with renal impairment:
ENEAS is contraindicated in patients with severe renal impairment (creatinine clearance below 10 ml/ min) or in patients on haemodialysis (see 4.3 and 4.4).

Children and adolescents:
There is no data on the administration of ENEAS in children and adolescents, therefore it should not be given to this patient group.

The tablets should be swallowed whole, without being broken or chewed, with sufficient quantity of water.

4.3 Contraindications

ENEAS should not be used in:

- Patients with hypersensitivity to enalapril, nitrendipine or to any of the excipients of the medicinal product.
- Patients with a history of angioedema related with the administration of angiotensin converting enzyme inhibitors or hereditary/idiopathic angioneurotic oedema.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Patients with unstable haemodynamic conditions, specially cardiovascular shock, acute heart failure, acute coronary syndrome, acute stroke.
- Patients with bilateral stenosis of the renal arteries or unilateral with only one kidney
- Haemodynamically relevant stenosis of the aortic or mitral valve and hypertrophic cardiomyopathy.
- Patients with severe renal impairment (creatinine clearance below 10 ml/min) and patients on haemodialysis.
- Patients with severe liver failure.

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

Concomitant use with sacubitril/valsartan therapy. Eneas must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

4.4 Special warnings and special precautions for use

Angioedema

Angioedema of the extremities, face, lips, mucous membranes, tongue, glottis or larynx may occur in patients treated with ACE inhibitors particularly during the first weeks of treatment. However, in rare cases, severe angioedema may develop after long-term treatment with an ACE inhibitor. Treatment should be discontinued promptly.

Angioedema involving the tongue, glottis or larynx may be fatal. Emergency therapy should be instituted. The patient should be hospitalised and observed for at least 12 to 24 hours, and should not be discharged until complete resolution of symptoms has occurred.

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 eneas. Treatment with eneas 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.

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 or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. If ENEAS is used in such patients, monitoring of differential white blood cell counts is advised. During treatment all patients should be instructed to report any sign of infection. ENEAS should be withdrawn if neutropenia (neutrophils less than 1000/mm^3) is detected or suspected.

Renal impairment
In patients with renal impairment, renal function should be monitored, particularly in the early weeks of treatment with angiotensin converting enzyme inhibitors (ACEI). Care should be taken in patients with activated renin-angiotensin system.

In patients with moderate renal impairment (creatinine clearance above 30 ml/min; serum creatinine ≤3 mg/ml), the dose does not need to be titrated, although renal function should be monitored.

In some patients, the onset of hypotension at the beginning of treatment with an ACE inhibitor may lead to a slight further deterioration of the renal function. In such circumstances, cases of acute renal impairment, generally reversible, have been observed.

There is no experience regarding the administration of ENEAS in patients with a recent kidney transplantation.

Proteinuria
In patients with pre-existing renal impairment proteinuria may occur rarely. In patients with clinically relevant proteinuria (greater than 1 g/day), ENEAS should only be used after critical benefit-risk evaluation and with regular monitoring of the clinical and laboratory chemical parameters.

Hepatic impairment
In patients with mild to moderate hepatic impairment neither enalapril nor nitrendipine in monotherapy are contraindicated, but as there is no experience regarding the administration of ENEAS in these cases, it should be given with caution if indicated to these patients. ENEAS is contraindicated in patients with severe hepatic impairment (see 4.3).

The elimination of nitrendipine may be slowed down because of liver failure especially in the elderly, this may cause undesirable hypotension.
As a syndrome beginning with cholestatic jaundice and progression to hepatic necrosis with fatal outcome has been described in isolated cases, in case of jaundice or marked rise in liver enzyme discontinuation of therapy and monitoring of patients is necessary.

Renovascular hypertension /renal arterial stenosis (see 4.3)
There is an increased risk of serious hypotension and renal impairment when ACE inhibitors are given to patients with renovascular hypertension, pre-existing bilateral renal arterial stenosis or unilateral arterial stenosis with only one functioning kidney. Loss of renal function may appear with only small changes in serum creatinine, even in patients with unilateral renal arterial stenosis.

Serum potassium
ACEIs may produce increases in serum potassium, particularly in patients with renal impairment and/or heart failure. Thus, the administration of potassium sparing diuretics or potassium supplements is not recommended. Should the concomitant use of these substances prove necessary, potassium serum levels must be monitored.

ACE inhibitors can cause hyperkalemia 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, hyperkalemia 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).

Hypotension

In certain cases, ENEAS may produce orthostatic hypotension, and this risk is increased in patients with activation of the renin-angiotensin-aldosterone system, such as cases of volume or salt depletion, due to the use of diuretics, low salt diet, haemodialysis, diarrhoea or vomiting; reduced left ventricle function; renovascular hypertension. Volume or salt depletion must be corrected first in these patients. In patients with heart failure, with or without associated renal impairment, symptomatic hypotension may appear. The onset of hypotension in these patients is more probable if major degrees of heart failure are present, they are given high doses of loop diuretics and they have hyponatremia or impaired renal function. These patients should be strictly monitored at the beginning of treatment. These considerations are applicable to patients with ischemic heart disease or cerebrovascular diseases in whom an excessive reduction in blood pressure could give rise to myocardial infarction or cerebrovascular accident.

If hypotension occurs the patient should be placed in the decubitus position and, if necessary, intravenous isotonic saline solution should be given. A transient hypotensive response is not a contraindication for continuing the treatment with ENEAS, which is generally free of difficulties once circulating volume and blood pressure have been restored.

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.

Outflow track obstruction

In patients with obstruction in the outflow tract of the left ventricle, ACEI should be used with caution. If the obstruction is haemodynamically relevant, enalapril maleate is contraindicated (see 4.3).

Cough

Coughing has been reported with the use of ACEI. It is a non-productive persistent cough that disappears when treatment is suspended.

Primary hyperaldosteronism

As a rule, patients with primary hyperaldosteronism do not respond to antihypertensive agents, whose effect is based on the inhibition of the renin-angiotensin system. Thus, the administration of enalapril maleate is not recommended.

Dyalised patients
Concomitant use of ENEAS and poly (acrylonitril, sodium-2-methylallyl sulphonate) high-flux-membranes (eg, "AN 69") in dialysed patients may lead to anaphylactic reactions such as facial swelling, flushing, hypotension and dyspnoea within a few minutes of commencing dialysis. This combination must therefore be avoided. ENEAS is contraindicated in dialysis patients (see 4.3).

Anaphylactoid reactions during LDL apheresis / during hymenoptera desensitisation
Patients with LDL (low density lipoproteins) apheresis with dextrane sulfate may experience life-threatening anaphylactoid reactions when taking ACEI. Patients taking an ACEI during specific immunotherapy (desensitisation) against insect poison (eg. bee or wasp stings) may experience anaphylactoid reactions (eg. reduction of blood pressure, dyspnea, vomiting and skin allergy), which in some cases may be life-threatening. If LDL apheresis or specific immunotherapy (desensitisation) against insect poison is required, the ACEI should be temporarily replaced by another medicinal product for hypertension or heart failure.

Surgery / Anaesthesia
In patients undergoing major surgery or during anaesthesia with hypotension-inducing agents, enalapril blocks the formation of angiotensin II induced by the compensatory release of renin. In these cases, if hypotension arises and is believed to be caused by this mechanism, it should be corrected by increasing plasma volume.

Fertility
In isolated cases of in vitro fertilisation, calcium antagonists such as nitrendipine have been associated with reversible biochemical changes in the head of spermatozoa, which may lead to an alteration of sperm function. In men, there are cases of repeat paternity failure of in vitro fertilization, and when no other explanation is available, calcium antagonists must be regarded as a possible reason.

Pregnancy:
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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).

Ethnic differences
As with other angiotensin converting enzyme inhibitors, enalapril, a component of the fixed-dose combinations, is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

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

4.5 Interaction with other medicinal products and other forms of interaction

The antihypertensive effect of ENEAS may be boosted by other antihypertensive medicinal products such as diuretics, beta-blockers or alpha-adrenergic blocking agents such as prazosine.

Furthermore, the following interactions may be caused by some of the ingredients of the

association:

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).

Combinations with precautions for use

Potassium sparing diuretics or potassium supplements or potassium-containing salt substitutes
ACEIs reduce potassium loss caused by diuretics. Potassium sparing diuretics, potassium supplements and other medicaments which may increase levels of serum potassium (eg, heparin) may have additive effects on serum potassium particularly in patients with impaired renal function.
If their concomitant use is indicated because of demonstrated hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium (see 4.4).

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with eneas. 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 eneas 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 eneas 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.

Lithium
The combination of enalapril with lithium should be not recommended, due to the risk of major increase of serum lithium levels, with severe neurotoxicity. If concurrent treatment with lithium salts is given, lithium serum concentrations should be closely monitored.

Non-steroidal antiinflammatories
Non-steroidal anti-inflammatory medicinal products and ACE inhibitors exert an additive effect on serum potassium increase, whereas renal function can decrease. When given to the elderly and/or dehydrated patients, this combination can lead to acute renal failure by acting directly on glomerular filtration. Moreover, concomitant treatment can reduce the antihypertensive effect of ACEIs.

Oral antidiabetics
The administration of enalapril may boost the hypoglycemiant effect of these substances, whereby blood glucose monitoring should be intensified.

Baclofene
It may increase antihypertensive activity. If necessary, blood pressure shall be monitored and the dose titrated.

Antipsychotics
Joint administration with these medicinal products may produce postural hypotension.

Antidepressants
Joint administration with triclyclic antidepressants may produce postural hypotension.

Alopurinol, cytostatics, immunosuppressors, systemic corticosteroids, procainamide
They may produce leukopenia.

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.

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).

Combinations to be considered

Amifostine
Increased antihypertensive effect.

Nitrendipine

Cimetidine and ranitidine
Cimetidine, and to a lesser extent ranitidine, may increase plasma levels of nitrendipine but the clinical relevance of these effects is not known.

Digoxin
Enalapril has been given with digoxin with no evidence of clinically significant adverse interactions. The simultaneous administration of nitrendipine and digoxin may lead to increased digoxin plasma levels. Therefore, patients should be supervised for symptoms of digoxin overdose or, as appropriate, the digoxin-plasma level should be monitored.

Muscular relaxants
The administration of nitrendipine may boost the duration and the intensity of the effects of muscular relaxants such as pancuronium.

Grapefruit juice inhibits the oxidative metabolism of nitrendipine. The simultaneous intake of the latter with grapefruit juice increases its plasma concentration, which may increase the hypotensive effect of the preparation.

Nitrendipine is metabolised by the cytochrome P450 3A4 system, located in the intestinal mucosa and in the liver. Active substances that induce this enzymatic system, such as anticonvulsants (eg. phenytoin, phenobarbital, carbamazepine) and rifampicine may lead to a major reduction in the bioavailability of nitrendipine. Moreover, active substances that inhibit

this enzymatic system (e.g. antifungal imidazoles like itraconazole and others) may produce an increase in nitrendipine plasma concentrations.

β-blockers
Nitrendipine and β-blockers have synergetic effects. This may be of special relevance in patients whose sympathetic vascular reactions could not be compensated in case of additional beta-blocking treatment, so caution is recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy:

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated 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 antihypertensive 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).

Lactation:
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 ENEAS 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 ENEAS 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.

4.7 Effects on the ability to drive and use machines

The administration of ENEAS may produce certain adverse reactions that reduce the state of alertness, hampering the ability to drive or use machines. This is particularly important at the beginning of treatment, when treatment is changed, and/or with the consumption of alcohol. Precaution is therefore recommended until a satisfactory response to the medicinal products is attained.

4.8 Undesirable effects

The adverse reactions observed following the administration of ENEAS are similar to those described for each one of the ingredients separately.

The most frequent ones are (Common 1-10%): flushing, oedema, headache and cough.

Uncommon adverse reactions (0.1-1%) are dizziness, tachycardia, erythematous rash, nausea, dyspepsia and hypotension. Very rare (<0.01%): Isolated cases of asthenia, hypotermia, palpitation, peripheral ischaemia, haematuria, pharingitis, tracheitis, dyspnoea, abdomen enlarged, hepatic enzymes increased, hypokalaemia, somnolence, parestesias, tremor and cramps possibly related to ENEAS have been reported in clinical trials.

The following adverse reactions have been associated with the use of either drug in monotherapy:

Enalapril maleate

Cardiovascular system:
Occasionally: especially at the beginning of therapy and in patients with salt and/or fluid deficiency, heart failure, severe or renal hypertension, but also after a dose increase of enalapril maleate and/or diuretics hypotension and/or orthostasis with symptoms such as dizziness, weakness, visual disorders and, rarely, syncope.
Isolated reports: in connection with an increased fall in blood pressure: tachycardia, palpitations, cardiac dysrhythmias, atrial bradycardia, atrial fibrillation, chest pain, angina pectoris, myocardial infarction, TIA, cerebrovascular accident. Cardiac arrest, embolism and pulmonary infarctation, pulmonary oedema.

Kidney:
Occasionally: occurrence or deterioration of renal function disorders, in isolated cases progression to acute renal failure.
Rarely: oliguria, proteinuria, in some cases with a concurrent deterioration in renal function, flank pain.

Respiratory tract:
Occasionally: dry cough, sore throat, hoarseness, bronchitis.
Rarely: dyspnoea, sinusitis, rhinitis.
Isolated cases: bronchospasm/asthma, pulmonary infiltrates, stomatitis, glosisitis, dry mouth, pneumonia, angioneurotic oedema involving the larynx, pharynx and/or tongue causing fatal airway obstruction in individual cases, with a greater incidence in black patients.

Gastrointestinal tract/liver:
Occasionally: nausea, upper abdominal pain, digestive disorders.
Rarely: vomiting, diarrhoea, constipation, loss of appetite.
Isolated cases: liver function disorders, hepatitis, liver failure, pancreatitis, ileus, stomatitis, glossitis, a syndrome beginning with cholestatic jaundice and progression to hepatic necrosis with fatal outcome in some cases.

Endocrine:
Isolated cases: gynecomastia.

Skin, vessels:
Occasionally: allergic skin reactions such as exanthema.
Rarely: urticaria, pruritus, angioneurotic edema involving lips, face and/or extremities.
Isolated cases: severe skin reactions such as pemphigus, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome or toxic epidermal necrolysis; changes resembling psoriasis, photosensitivity, flushing, diaphoresis, alopecia, onycholysis and worsening of

Raynaud's disease. Skin changes may be accompanied by fever, myalgia/myositis, arthralgia/arthritis, vasculitis, serositis, eosinophilia, leucocytosis, increased ESR and/or raised ANA titres. If a severe skin reaction is suspected therapy should be terminated.

Nervous system:
Occasionally: headache, fatigue.
Rarely: giddiness, depression, sleep disorders, impotence, peripheral neuropathy with paraesthesia, disturbed balance, muscle cramps, nervousness, confusion.

Sensory organs:
Rarely: tinnitus, blurred vision, changes in taste perception or translient loss of taste, anosmia, dry eyes, tearing.

Laboratory parameters:
Occasionally: reduction in haemoglobin, haematocrit and leukocyte or platelet count.
Rarely: especially in patients with impaired renal function, collagen disease or in those receiving allopurinol, procainamid or immunosuppressants, anaemia, thrombocytaemia, neutropenia, eosinophilia (in isolated cases agranulocytosis or pancytopenia); specially in patients with impaired renal function, severe heart failure and renovascular hypertension increase of serum concentrations of urea, creatinine and potassium, decrease of sodium serum concentration, hyperkalaemia (in diabetic patients), increased excretion of albumin in urine.
Isolated reports: haemolysis/haemolytic anaemia (also in connection with G-6-PDH deficiency), increase in bilirrubin and liver enzyme concentrations.

Nitrendipine

General:
Occasionally: asthenia, flu symptoms.

Cardiovascular:
Occasionally: arrhythmia, tachycardia, palpitation, peripheral oedema, flushing, vasodilation.
Rarely: hypotension, angina pectoris, chest pain.

Digestive:
Occasionally: nausea, diarrhoea. Rarely: abdominal pain, constipation, dyspepsia, vomiting; isolated cases: gingival hyperplasia.

Endocrine:
Isolated cases: gynecomastia.

Haematological:
Isolated cases: leukopenia, agranulocytosis.

Musculo-skeletal:
Rarely: myalgia.

Central Nervous System:
Occasionally: headache. Rarely: nervousness, paresthesia, tremors, vertigo

Respiratory:
Rarely: dyspnoea

Skin:

Rarely: itching, rash, urticaria

Sensory organs:
Rarely: altered vision.

Urogenital:
Isolated cases: increased urinary frequency, polyuria.

Laboratory parameters:
Isolated cases: increase in liver enzyme concentrations

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 national reporting system listed in Appendix V

4.9 Overdose

Hitherto, no cases of overdosage with this association have been reported.
The most probable manifestation of overdosage with ENEAS would be hypotension.

Management
Primary detoxification by gastric lavage, administration of adsorbens and/or sodium sulphate (if possible during the first 30 minutes). Vital functions should be monitored.
In case of hypotension, the patient should be placed in shock position and salt and volume replacement should be carried out initially. If there is no response, catecholamines should then also be given intravenously. Therapy with angiotensin II may be considered.
Bradycardia should be treated administering atropine. The use of a pacemaker may be considered.
Serum electrolyte and serum creatinine concentrations must be constantly monitored.
Enalapril is dialysable at a rate of 62 ml/ min, but the use of high-flux polyacrylonitrile membranes must be avoided (see 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacoterapeutic group: Angiotensin Converting Enzyme (ACE) inhibitors and calcium channel blockers.
ATC Code : C09B B06

The two active substances of ENEAS have complementary antihypertensive actions.

ACE is a peptidyl dipeptidase that catalyses the conversion of angiotensin I into the pressor substance angiotensin II. Once absorbed, enalapril is transformed by hydrolysis into enalaprilate, a substance that inhibits ACE. This inhibition results in a reduction of angiotensin II in plasma, which leads to increased activity of plasma renin (on suppressing the mechanism of negative retroaction for the release of renin) and a reduction in the secretion of aldosterone.

While it is believed that the mechanism whereby enalapril reduces blood pressure is mainly the inhibition of the renin-angiotensin-aldosterone system, which plays a basic role in the regulation of blood pressure, enalapril has antihypertensive action even in cases of hypertension with low renin.

The prolonged administration of enalapril to patients with essential hypertension and renal impairment may result in an improvement of renal function in the form of an increase in the rate of glomerular filtration.

Nitrendipine is a calcium antagonist of the dihydropyridine1-4 group that acts as an antihypertensive agent. The mechanism of action of nitrendipine lies in the inhibition of the flow of calcium ions to the vascular smooth muscular tissue. This action has the following pharmacological effects: protection against increased flow of calcium into the tissue, inhibition of vascular muscular contraction dependant on myogenic calcium, reduction of peripheral vascular resistance, reduction of pathologically high blood pressure and mild natriuretic effect, particularly at the beginning of the treatment.

In phase III clinical trials carried out with ENEAS in hypertensive patients who did not respond to monotherapy with 10 mg enalapril or with 20 mg nitrendipine, greater efficacy of ENEAS was observed in reduction of both the diastolic and systolic blood pressure, as well as in the rate of response to treatment.

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."

5.2 Pharmacokinetic properties

Enalapril given p.o. is rapidly absorbed and reaches maximum serum concentrations within an hour. The amount absorbed is 60% of the dose given and is not affected by the intake of food.
Plasma protein binding is 50-60%.

Following absorption, enalapril is rapidly and extensively converted, by hydrolysis, into enalaprilate, a potent inhibitor of the angiotensin converting enzyme. Enalaprilate reaches maximum concentrations in serum three to four hours after an oral dose of enalapril. Enalaprilate is excreted mainly via the kidney. The main ingredients in urine are enalaprilate, which accounts for approximately 40% of the dose given, and intact enalapril. Barring its conversion into enalaprilate, there are no signs of any other significant metabolic transformation of enalapril.

The serum concentration curve shows a prolonged terminal phase apparently associated with its binding to the ACE. In subjects with normal renal function, the serum concentrations of enalaprilate reached steady-state on the fourth day of administration of enalapril. The effective half-life for the accumulation of enalaprilate following the administration of repeated doses of enalapril p.o. is 11 hours. The percentage of absorption and hydrolysis of enalapril is similar with all the recommended therapeutic doses.

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.

Nitrendipine is absorbed quickly and almost completely (88%). Maximum plasma concentrations are reached between 1 and 3 hours after administration.

Bioavailability is 20-30% due to a considerable first-pass effect. Nitrendipine binds to plasma proteins (albumin) between 96-98%, and is therefore not dialyzable. The distribution volume in steady state is approximately 5-9 l/kg, therefore haemoperfusion or plasmapheresis are not efficacious.

Nitrendipine is metabolised almost completely in the liver, mainly by oxidative processes. The metabolites are inactive. Less than 0.1% of the oral dose is excreted as unchanged nitrendipine in urine. Nitrendipine is excreted mainly through the kidney in the form of metabolites (about 77% of the oral dose), and the rest through the biliary route in faeces.

The elimination half-life of nitrendipine tablets is between 8 and 12 h. No accumulation of the active substance or its metabolites has been observed. In patients with chronic liver disease elevated plasma levels were observed, since nitrendipine is eliminated mainly metabolically. However, there is no need for dose titration in patients with altered renal function.

The results of interaction studies in healthy volunteers, when enalapril and nitrendipine were given concomitantly, showed no interaction for nitrendipine.
For enalaprilat bioavailability was slightly higher after administration of the combination but this seems to have no clinical relevance. In comparison to the free combination the bioavailability of nitrendipine when given as fixed combination is increased.

5.3 Preclinical safety data

No studies of safety pharmacology, reprotoxicity, genotoxicity and carcinogenesis were conducted with the association of enalaprilate and nitrendipine (1:2).

In single- and repeat-dose toxicity studies (26 weeks), conducted in rats and dogs with enalapril and nitrendipine (1:1) at tolerable doses, no differences were observed in the onset of toxic effects after the administration of both active substances in association, versus the toxic effects described when each individual ingredient was administered separately.

Enalapril and nitrendipine are known active substances with a well-established therapeutic use, which present no evidence of mutagenic and carcinogenic potential, whereupon this association is not expected to present an added potential risk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate.
Lactose monohydrate.
Microcrystalline cellulose.
Maize starch.
Povidone.
Sodium lauryl sulphate.
Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Blister Aluminium/Aluminium: 3 years. Strip Aluminium/Aluminium: 2 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Blisters comprising a polyamide-PVC-aluminium foil complex and an aluminium foil or strip comprising two aluminium foils.
Container with 20 tablets
Container with 30 tablets
Container with 50 tablets
Container with 60 tablets
Container with 100 tablets
Container with 300 tablets
Container with 500 tablets
Not all pack sizes may be marketed.

6.6 Instructions for use/handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

FERRER INTERNACIONAL S.A.
Gran Vía de Carlos III, 94
08028 – Barcelona
SPAIN

8. MARKETING AUTHORIZATION NUMBER

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Janurary 2002 / March 2007

10. DATE OF REVISION OF THE TEXT

December 2015

ENEAS-SPC6
March 2019