PACKAGE INSERT

SCHEDULING STATUS

S3

PROPRIETARY NAME (AND DOSAGE FORM)

ENVAS 5 tablets

ENVAS 10 tablets

COMPOSITION

Each **ENVAS 5** tablet contains 5 mg enalapril maleate.

Each **ENVAS 10** tablet contains 10 mg enalapril maleate.

PHARMACOLOGICAL CLASSIFICATION

A 7.1.3 Other hypotensives.

PHARMACOLOGICAL ACTION

ENVAS inhibits angiotensin I - converting enzyme (ACE) activity. It inhibits the conversion of the relatively inactive angiotensin I to the active angiotensin II. Angiotensin II is a potent vasoconstrictor and stimulates the release of aldosterone. Decreased angiotensin II levels result in a decrease in vasopressor activity and a reduction in aldosterone secretion, which may result in small increases in serum potassium. It is also thought that ACE inhibition may inhibit degradation of bradykinin, leading to increased bradykinin levels.

Pharmacokinetics:

Enalapril acts as a pro -drug of the di acid enalaprilat, its active form, which is poorly absorbed by mouth.

About 60 % of an oral dose of enalapril is absorbed from the gastrointestinal tract and peak plasma concentrations are achieved within about 1 hour. Enalapril is extensively hydrolysed

in the liver to enalaprilat; peak plasma concentrations of enalaprilat are achieved 3 to 4 hours after an oral dose of enalapril. Enalaprilat is 50 to 60 % bound to plasma proteins. After an oral dose, enalapril is excreted in the urine and in faeces, as enalaprilat and unchanged drug, with the urinary route predominating; more than 90 % of an intravenous dose of enalaprilat is excreted in the urine. The elimination of enalaprilat is multiphasic but the effective half - life for accumulation after multiple doses of enalapril is reported to be about 11 hours in patients with normal renal function. Enalaprilat is removed by haemodialysis and by peritoneal dialysis.

INDICATIONS:

ENVAS is indicated in:

- **Hypertension**

  All grades of essential hypertension and renovascular hypertension

- **Heart failure**

  ENVAS is indicated for the treatment of symptomatic congestive heart failure, usually in combination with diuretics and digitalis. In these patients **ENVAS** improves symptoms, increases survival, and decreases the frequency of hospitalization (see **PHARMACOLOGICAL ACTION** for details).

- **Asymptomatic Left Ventricular Dysfunction**

  In clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction< 35 %) **ENVAS** decreases the rate of development of overt heart failure and decreases the incidence of hospitalization for heart failure.

CONTRA-INDICATIONS

- Hypersensitivity to any of the components of **ENVAS**.
- Patients with a history of angioedema related to previous ACE-inhibitor therapy or angiotensin receptor blockers.

- Hereditary or idiopathic angioedema.
- Aortic stenosis.
- Hypertrophic obstructive cardiomyopathy.
- Severe renal function impairment (creatinine clearance below 30 ml/min)
- Renal artery stenosis in patients with a single kidney.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride.
- Porphyria.

WARNINGS

Should a woman become pregnant while receiving an ACE inhibitor, the treatment must be stopped promptly and changed to a different medicine (see **PREGNANCY AND LACTATION**).

If a woman is contemplating pregnancy, a different class of medicine should be used (see **PREGNANCY AND LACTATION**).

ENVAS should be used with caution in the following conditions:

- Cerebrovascular disease or ischemic heart disease Reduction in blood pressure could aggravate these conditions and may result in myocardial infarction and cerebrovascular incidents.
- Volume depleted patients (e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting) Although it may occur in normovolaemic patients, hypotension is more likely in volume depleted patients. A sudden reduction in angiotensin II may result in sudden and severe hypotension. There is also an increased risk of **ENVAS** induced renal failure, especially in those with congestive heart failure.
- Patients at a high risk of symptomatic hypotension e.g. patients with salt or volume depletion with or without hyponatremia should have these conditions corrected before therapy with **ENVAS**. Monitoring is required after initiating therapy.

- Autoimmune disease, especially systemic lupus erythematosus, other collagen vascular disease or scleroderma: Increase the risk for development of neutropenia or agranulocytosis.
- In acute myocardial infarction, treatment with **ENVAS** should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentrations exceeding 177 µmol/l or proteinuria exceeding 500 mg/24 hours). If renal dysfunction develops during treatment (serum creatinine concentrations exceeding 177 µmol/1 or doubling ofthe pre -treatment value) then **ENVAS** may need to be withdrawn (see **CONTRA INDICATIONS**).
- In acute myocardial infarction, patients may develop persistent hypotension and/or impaired renal function.
- Hypotension in acute myocardial infarction -treatment with **ENVAS** must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These include patients with systolic blood pressure of 100 mm Hg or lower or cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mm Hg or lower. Maintenance doses should be reduced to 5 mg or temporarily to2,5 mg if systolic blood pressure is 100 mm Hg or lower. If hypotension persists (systolic blood pressure less than 90 mm Hg or more than 1 hour) then **ENVAS** should be withdrawn.
- Bone marrow depression - Increased risk of agranulocytosis and neutropenia.
- Diabetes mellitus - Increased risk of hyperkalaemia, as well as hypoglycaemia may occur.
- Hyperkalaemia - **ENVAS** may cause an increase in serum potassium levels.
- Renovascular disease - **ENVAS** should not be used in patients with renovascular disease or suspected renovascular disease but it may be used cautiously in severe resistant hypertension in such patients. In this instance **ENVAS** should only be used under specialist supervision. The elderly, patients with peripheral vascular diseases or generalised atherosclerosis may have asymptomatic renovascular disease (see **DOSAGE AND DIRECTIONS FOR USE**).

- Renal artery stenosis, bilateral or in one kidney or renal transplant Increased risk of further renal function impairment (see **CONTRA-INDICATIONS**).
- There is also an increased risk of agranulocytosis and neutropenia when immunosuppressants are concurrently administered.
- Renal function impairment - Decreased elimination of **ENVAS** resulting in an increased risk of hyperkalaemia. These patients may require lower doses.
- Anaphylactoid reactions have occurred in patients using ACE inhibitors during desensitising protocols involving for example, hymenoptera venom.
- Anaphylactoid reactions have been reported in patients exposed to either high -flux membrane dialysis or low-density lipoprotein apheresis with dextran sulfate absorption.
- Hypersensitivity/ angioedema - If angioedema of the face, extremities, lips, tongue, glottis and/or larynx is observed in patients treated with **ENVAS**, **ENVAS** should be discontinued promptly. These patients should be monitored to ensure complete resolution of symptoms.
- Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, it is likely to cause airway obstruction, and appropriate emergency therapy should be administered. This may include the administration of adrenaline (epinephrine) and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred. **These patients should never receive ENVAS or any other ACE Inhibitor again.**
- **ENVAS** causes a higher rate of angioedema in black patients than in non-black patients.
- Safety and efficacy in children has not been established.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride may lead to hyperkalaemia, which may be severe and lead to cardiac conduction abnormalities, dysarrhythmias and cardiac arrest.

INTERACTIONS

Concomitant use of **ENVAS** with:

- Diuretics, alcohol and hypotension-producing medications The antihypertensive effect is additive. Dosage adjustments may be necessary during concurrent use or when one medicine is discontinued.
- Loop, thiazide or related diuretics "First dose hypotension" may occur (see **DOSAGE AND DIRECTIONS FOR USE**).
- Indomethacin and non -steroidal anti-inflammatory medicines (NSAIDs) - reduce the antihypertensive effects of **ENVAS**. Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with **ENVAS**.
- Potassium supplements or potassium sparing diuretics such as spironolactone, triamterene or amiloride. Concurrent administration may result in hyperkalaemia
- Lithium Increases in lithium concentrations have been reported. Frequent monitoring of serum lithium concentrations is recommended.

PREGNANCY AND LACTATION

Use of **ENVAS** limited to the first trimester does not appear to present a significant risk to the foetus, but foetal exposure after this time has been associated with teratogenicity and severe toxicity in the foetus and newborn, including death. **ENVAS** crosses the placenta. Foetal exposure to ACE inhibitors during the second and third trimester can cause hypotension, renal failure, anuria, skull hypoplasia, hyperkalaemia and oliguria. Oligohydramnios may occur resulting in pulmonary hypoplasia, limb contractures and craniofacial deformation. Infants who have been exposed in utero to **ENVAS** should be closely monitored. Peritoneal dialysis may be of some benefit in the clearance of **ENVAS** from the neonatal circulation. Safety in lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

May be taken with/without meals preferably at the same time every day.

Essential Hypertension

The initial dose is 10 to 20 mg depending on the degree of hypertension and is given once daily. In mild hypertension the recommended initial dose is 10 mg daily. For other degrees of hypertension the initial dose is 20 mg daily. The usual maintenance dose is one 20 mg tablet taken once daily. The dosage should be adjusted according to the needs of the patient.

Renovascular Hypertension

Since blood pressure and renal function in such patients may be particularly sensitive to ACE-inhibition, therapy should be initiated with a lower starting dose (eg. 5 mg or less). The dosage should then be adjusted according to the needs of the patient. Most patients may be expected to respond to one 20 mg tablet, taken once daily. For patients with hypertension who have been treated recently with diuretics, caution is recommended.

Concomitant Diuretic Therapy In Hypertension

Symptomatic hypotension may occur following the initial dose of **ENVAS**. This is more likely in patients who are being treated currently with diuretics.

Caution is recommended, therefore, since these patients may be volume or salt depleted. The diuretic therapy should be discontinued for 2 - 3 days prior to initiation of therapy with **ENVAS**. If this is not possible. the initial dose of **ENVAS** should be low (5 mg or less) to determine the initial effect on the blood pressure. Dosage should then be adjusted according to the needs of the patient.

Dosage in Renal Insufficiency

Generally, the intervals between the administration of enalapril should be prolonged and/or the dosage reduced.

Renal Status	Creatinine Clearance ml/min	Initial dose per day
Mild Impairment	>30 to <80	5 - 10 mg
Moderate Impairment	>10 to ≤30	2,5 mg
Severe Impairment[1]	≤10	2,5 mg on dialysis days

[1]Normally, these patients will be on dialysis.

Enalaprilat is dialysable. Dosage on non-dialysis days should be adjusted depending on the blood pressure response.

Heart Failure/Asymptomatic Left Ventricular Dysfunction

The initial dose of **ENVAS** in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2,5 mg, and it should be administered under close medical supervision to determine the initial effect on the blood pressure. In the absence of, or after effective management of, symptomatic hypertension following initiation of therapy with **ENVAS** in heart failure, the dose should be increased gradually to the usual maintenance dose of 20 mg, given in a single dose or two divided doses, as tolerated by the patient.

This dose titration may be performed over a 2 to 4 week period, or more rapidly ff indicated by the presence of residual signs and symptoms of heart failure. In patients with symptomatic heart failure, this dosage regimen was effective in reducing mortality.

Blood pressure and renal function should be monitored closely before and after starting treatment with **ENVAS** (see **SPECIAL PRECAUTIONS**) because hypotension and consequent renal failure have been reported. In patients treated with diuretics, the dosage should be reduced if possible before beginning treatment with **ENVAS**. The appearance of hypotension after the initial dose of **ENVAS** does not imply that hypotension will recur during chronic therapy with **ENVAS** and does not preclude continued use of **ENVAS**. Serum potassium also should be monitored (see **INTERACTIONS**).

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects:

Haematological:

Less frequent:

Decrease in white blood cell count, haemoglobin and haematocrit, bone marrow depression, anaemia, thrombocytopenia, agranulocytosis, haemolytic anaemia

Cardiovascular:

Less frequent:

Orthostatic effects including hypotension. myocardial infarction, cerebrovascular incident, palpitations, tachycardia.

Neurological:

Frequent:

Dizziness, headache, fatigue.

Less frequent:

Mood alterations, mental confusion, paraesthesia, vertigo sleep disturbances.

Hyperkalaemia, hyponatraemia, increases in blood urea, increases in serum creatinine.

Gastrointestinal disorders:

Frequent:

Diarrhoea, nausea.

Less frequent:

Abdominal pain; indigestion; dry mouth, pancreatitis, vomiting, taste disturbances.

Kidney/Genitourinary:

Less frequent:

Uraemia, oligouria, anuria, renal dysfunction, acute renal failure, impotence.

Liver/Hepatic:

Less frequent:

Hepatitis (hepatocellular or cholestatic) with or without jaundice, increases in liver enzymes, increases in serum bilirubin.

Musculoskeletal disorders:

Less frequent:

Asthenia.

Respiratory:

Frequent:

Cough.

Less frequent:

Bronchospasm, rhinitis, sinusitis.

Skin disorders:

Less frequent:

Rash; urticaria; diaphoresis; alopecia; pruritus; psoriasis; severe skin disorders. including pemphigus, toxic epidermal necrolysis, Stevens Johnson Syndrome and erythema multiforme.

Other:

Less frequent:

Hypersensitivity/angioedema reactions: angioedema of the face, which may be fatal, extremities, lips, tongue, glottis and/or larynx and intestinal angioedema. A symptom complex has been reported which may include: fever, vasculitis, myalgia, arthritis/arthralgia, a positive antinuclear antibodies (ANA), elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

Special precautions:

Myocardial infarction and cerebrovascular accidents may be due to severe falls in blood pressure in high risk patients e.g. those with ischaemic heart disease or cerebrovascular disease.

In volume depleted patients or patients with ischaemic heart disease or cerebrovascular disease, therapy should be monitored especially when the dose of **ENVAS** or diuretic is adjusted.

If hypotension occurs, the patient should be placed in the suprine position and if necessary receive an intravenous infusion of 0,9 % saline.

Increases in blood urea and serum creatinine have been seen in patients with no apparent pre-existing vascular disease, especially when **ENVAS** has been given concomitantly with a diuretic. Dosage reduction or discontinuation of **ENVAS** or the diuretic may be required.

Signs of facial or extremity swelling or difficulty in swallowing or breathing, required immediate medical attention, because of the risk of angioedema.

Caution when driving or performing tasks requiring alertness because of possible dizziness.

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(See **Side-effects and Special Precautions**)

Symptoms of overdose:

Severe hypotension, electrolyte disturbances and renal failure.

Treatment of overdose:

Treatment is symptomatic and supportive. Activated charcoal may be given in severe overdosage if the patient presents within 1 hour of ingestion. Treatment consists of volume

expansion to correct hypotension and treating dehydration and electrolyte imbalances. **ENVAS** is removable by haemodialysis.

IDENTIFICATION

ENVAS 5: A white, round, flat beveled edge uncoated tablet with a breakline on the one side.

ENVAS 10: A light pink coloured, round, flat beveled edge uncoated tablet with a breakline on the one side.

PRESENTATION

ENVAS 5 / 10 tablets are available in unit cartons containing 3 x 10 (30's), 10 x 10 (100's) or 2 x 14 (28’s) aluminium foil strip packs.

STORAGE

Store in a dry place below 25 °C. Protect from light.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER

ENVAS 5: 34/7.1.3/0335

ENVAS 10: 34/7.1.3/0336

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