

pharmaniaga™



Enalapril

Tablet

DESCRIPTION

Pharmaniaga Enalapril tablet 5 mg

White, barrel shaped tablets, with Pharmaniaga icon on one side and scored on the other.

Pharmaniaga Enalapril tablet 20 mg

Peach, barrel shaped tablets, with Pharmaniaga icon on one side and scored on the other.

COMPOSITION

Pharmaniaga Enalapril tablet 5 mg

Each tablet contains Enalapril maleate 5 mg.

Pharmaniaga Enalapril tablet 20 mg

Each tablet contains Enalapril maleate 20 mg.

ACTIONS

Enalapril after hydrolysis to enalaprilat, inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyses the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of enalapril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion.

While the mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, enalapril is antihypertensive even in patients with low-renin hypertension.

Following oral administration of enalapril maleate peak serum concentrations of enalapril occur within about one hour. Based on urinary recovery, the extent of absorption of enalapril is approximately 60%. Enalapril absorption is not influenced by the presence of food in the gastrointestinal tract. Following absorption, enalapril is hydrolysed to enalaprilat, which is a more potent angiotensin converting enzyme inhibitor than enalapril; enalaprilat is poorly absorbed when administered orally.

Peak serum concentrations of enalaprilat occur three to four hours after an oral dose of enalaprilat maleate. Excretion of enalapril maleate is primarily renal. Approximately 94% of the dose is recovered in the urine and faeces as enalaprilat or enalapril. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril. There is no evidence of metabolites of enalapril, other than enalaprilat. Enalaprilat is 50 to 60% bound to plasma proteins; its elimination is multiphasic but its effective half-life for accumulation following multiple doses of enalapril is reported to be about 11 hours in patients with normal renal function.

INDICATIONS

- For the treatment of all grades of essential hypertension & renovascular hypertension.
- For the treatment of all degree of heart failure: In patients with symptomatic heart failure, enalapril maleate is indicated to improve survival and to retard the progression of heart failure.
- For the prevention of symptomatic heart failure: In asymptomatic patients with left ventricular dysfunction, enalapril maleate is indicated to retard the development of symptomatic heart failure.
- For the prevention of coronary ischemic events: In patients with left ventricular dysfunction, enalapril maleate is indicated to reduce the incidence of myocardial infarction.

CONTRAINDICATIONS

Enalapril maleate is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema.

Contraindicated during pregnancy as it can cause foetal and neonatal morbidity and mortality.

ADVERSE REACTIONS/ SIDE EFFECTS

Dizziness and headache were the more commonly reported side effects. Fatigue and asthenia were reported in 2-3% of patients. Other side effects occurred in less than 2% of patients, and included hypotension, orthostatic hypotension, syncope, nausea, diarrhoea, muscle cramps, rash and cough. Less

frequently renal dysfunction, renal failure, and oliguria have been reported.

Hypersensitivity / Angioneurotic Oedema

Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely.

Side effects which occurred very rarely, either during controlled clinical trials or after the drug was marketed, include:

Cardiovascular: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients such as chest pain, palpitations, rhythm disturbances, angina pectoris.

Gastrointestinal: ileus, pancreatitis, hepatic failure, hepatitis – either hepatocellular or cholestatic, jaundice, abdominal pain, vomiting, dyspepsia, constipation, anorexia, stomatitis.

Nervous System/ Psychiatric: depression, confusion, somnolence, insomnia, nervousness, paraesthesia and vertigo.

Respiratory: pulmonary infiltrates, bronchospasm/asthma, dyspnoea, rhinorrhoea, sore throat and hoarseness.

Skin: diaphoresis, erythema multiforme, exfoliative dermatitis, Steven-Johnson Syndrome, toxic epidermal necrolysis, pemphigus, pruritus, urticaria, alopecia.

Other: impotence, flushing, taste alteration, tinnitus, glossitis, blurred vision.

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

PRECAUTIONS

Symptomatic hypotension

Symptomatic hypotension was seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving enalapril, 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. 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, hyponatraemia 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 systemic blood pressure may occur with enalapril. This effect is anticipated and usually is not a reason to discontinue the treatment. If hypotension becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or enalapril may be necessary.

Hypersensitivity/ Angioneurotic Oedema

Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/ or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including enalapril. This may occur at any time during treatment. In such cases, enalapril should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioneurotic oedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy such as subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be administered promptly.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor.

Anaphylactoid Reactions During Hymenoptera Desensitisation

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

Haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Renal Function Impairment

In some patients hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

Patients with renal insufficiency may require reduced and/ or less frequent doses of enalapril. In some patients, with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases of blood urea and serum creatinine, reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency.

Some patients with no apparent pre-existing renal disease, have developed usually minor and transient increases in blood urea and serum creatinine when enalapril has been given concomitantly with a diuretic. Dosage reduction and/or discontinuation of the diuretic and/ or enalapril may be required.

Cough

Cough has been reported with the use of ACE inhibitors.

Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/ Anaesthesia

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

Porphyria

Enalapril has been associated with clinical exacerbations of porphyria and is considered unsafe in porphyric patients.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis, and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Aortic Stenosis/ Hypertrophic Cardiomyopathy

As with all vasodilators, enalapril should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

Warning

Increased risk of birth defects, foetal and neonatal morbidity and death when used throughout pregnancy.

Use in Pregnancy

The use of enalapril during pregnancy is not recommended. When pregnancy is detected, enalapril should be discontinued as soon as possible unless it is considered life saving for the mother.

ACE inhibitor can cause foetal and neonatal morbidity and mortality when administered to pregnant women during the second third trimesters. Use of ACE inhibitors during this period has been associated with foetal and neonatal injury including hypotension, renal failure, hyperkalaemia, and/or skull hypoplasia in the newborn. Maternal oligohydramnios, presumably representing decreased foetal renal function, has occurred and may result in limb contractures, craniofacial deformations and hypoplastic lung development. If enalapril is used the patient should be apprised of the potential hazard to the foetus.

These adverse effects to the embryo and foetus do not appear to have resulted from intrauterine ACE inhibitor exposure limited to the first trimester.

In those rare cases where ACE inhibitor use during pregnancy is deemed essential, serial ultrasound examinations should be performed to assess the intraamniotic environment. If oligohydramnios is detected, enalapril should be discontinued unless it is considered life saving for the mother. Patients and physicians should be aware; however, that oligohydramnios may not appear until after the foetus has sustained irreversible injury.

Infants whose mothers have taken enalapril should be closely

observed for hypotension, oliguria and hyperkalaemia. Enalapril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Use in Lactation

Enalapril and enalaprilat are secreted in human milk in trace amounts. Caution should be exercised if enalapril is given to a nursing mother.

Paediatrics

Use of enalapril has not been studied in children.

Effects on Ability to Drive and use Machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

Drug Interactions

Diuretic Therapy:

Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimised by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril.

If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilised for at least an additional hour.

Agents Causing Renin Release

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

Non-steroidal Anti-inflammatory Agents

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of enalapril may result in a further deterioration of renal function. These effects are usually reversible.

Agents Increasing Serum Potassium

Enalapril attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene or amiloride); potassium supplements or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium sparing agents should generally not be used in patients with heart failure receiving enalapril.

Lithium

Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

DOSAGE AND ADMINISTRATION

Essential hypertension: Initially 10-20 mg/ day. Maintenance: 20 mg once daily. Max: 40 mg/ day.

Renovascular hypertension: Initial: ≤ 5 mg.

Maintenance: Adjust according to patient's need. Usually 20 mg once daily.

Concomitant diuretic therapy in hypertension: Discontinue diuretic 2-3 days prior to initiation of therapy. If this is not possible, initial dose should be ≤ 5 mg.

Dosage in renal insufficiency: Generally, the intervals between the administration of enalapril should be prolonged and/or the dosage reduced.

SHELF LIFE

Product should not be used beyond the expiry date imprinted on the product packaging.

PRESENTATION

Pharmaniaga Enalapril tablet 5 mg and 20 mg
In blisters of 10, 30, 100 and 250 tablets.

Renal status	Creatinine Clearance mL/min	Initial Dose mg/day
Mild impairment	< 80 > 30 mL/min	5 - 10 mg
Moderate impairment	≤ 30 > 10 mL/min	2.5 - 5 mg
Severe impairment. Normally, these patients will be on dialysis.	≤ 10 mL/min	2.5 mg on dialysis days. Enalaprilat is dialysable. Dosage on nondialysis days should be adjusted depending on the blood pressure response.

Heart failure/ Asymptomatic LVD: Starting dose 2.5 mg. Usual maintenance dose: 20 mg daily given in single or 2 divided doses.

ROUTE OF ADMINISTRATION

Oral.

OVERDOSAGE

Limited data are available for overdosage in humans. The most prominent features of overdosage reported to date are marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockage of the renin-angiotensin system, and stupor. 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.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If ingestion is recent, induce emesis. Enalaprilat may be removed from the general circulation by haemodialysis.

STORAGE CONDITIONS

Pharmaniaga Enalapril Tablet5mg and 20mg

Store below 30°C.

Protect from light.

Date of revision: 17th November 2017

PRODUCT REGISTRATION HOLDER / MANUFACTURER:
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