ENAPRIL® TABLET

Presentation(s):
Enapril tablet 10mg:
Each tablet contains:
Enalapril maleate ……10mg
Enapril tablet 20mg:
Each tablet contains:
Enalapril maleate …… 20mg

Pharmacology (Summary of Pharmacodynamics and Pharmacokinetics):
Enalapril maleate is the maleate salt of enalapril, a derivative of 2 amino acids, L-alanine and L-proline. Following oral administration, enalapril is rapidly absorbed and then hydrolysed to enalaprilat, which is a highly specific, long- acting, non- sulfhydryl angiotensin- converting enzyme (ACE) inhibitor. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion.
Following oral administration of enalapril, peak serum concentrations occur within about one hour. Based on the urinary recovery, the extent of absorption is approximately 60%. Enalapril absorption is not influenced by the presence of food in the gastrointestinal tract. Peak serum concentrations of enalaprilat occur three to four hours after an oral dose of enalapril maleate. Excretion of enalapril is primarily renal. Approximately 94% of the dose is recovered in the urine and feces as enalaprilat or enalapril. The effective half-life for accumulation of enalaprilat following multiple doses of enalapril maleate is 11 hours.

Indication(s):
Essential and renovascular hypertension; congestive heart failure; prevention of symptomatic heart failure and coronary ischemic events in patient with left ventricular dysfunction.

Dosage and Administration:
Essential hypertension: Initially 10-20mg/day. Maintenance: 20mg once daily. Max: 40mg/day.
Renovascular hypertension: Initial ≤ 5mg. Maintenance: Adjust according to patient's need. Usually 20mg 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 ≤ 5mg. Dosage adjustment in renal impairment. Usual starting dose: 2.5-10mg depending on renal status.
Heart failure/ Asymptomatic LVD: Starting dose 2.5mg. Usual maintenance dose; 20mg daily given in single or 2 divided doses.
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 (mg/day)
Mild Impairment	<80 >30	5 - 10
Moderate Impairment	≤30 >10	2.5 – 5
Severe Impairment Normally, these patients will be on dialysis.*	≤10	2.5mg on dialysis days**
*See Hemodialysis Patients under Precautions. ** Enalaprilat is dialyzable. Dosage on non-dialysis days should be adjusted depending on the blood pressure response.		

Route of administration:
Oral administration

Contraindication(s):
Enalapril is contraindicated in patients who are hypersensitive to any component of enalapril and in patients with a history of angioneurotic edema relating to previous treatment with an angiotensin-converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema.

Precaution(s) / Warning(s):
a) *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. 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. In these patients, therapy should be started under medial 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.

   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 treatment. If hypotension becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or enalapril may be necessary.

b) *Aortic Stenosis, Hypertrophic Cardiomyopathy:* As with all vasodilators, ACE inhibitors should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

c) *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.

d) *Hypersensitivity/Angioneurotic Edema:* Angioneurotic edema 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.

e) *Anaphylactoid Reactions During Hymenoptera Desensitization:* Rarely, patients receiving ACE inhibitors during desensitization with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each desensitization.

f) *Hemodialysis Patients:* Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (eg, AN 69) 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.

g) *Cough:* Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy.

h) *Surgery/Anesthesia:* In patients undergoing major surgery or during anesthesia 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.

i) *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. If enalapril is used, the patient should be apprised of the potential hazard to the fetus.

j) *Use in lactation:* Nursing Mothers: Enalapril and enalaprilat are secreted in human milk in trace amounts. Caution should be exercised if enalapril is given to a nursing mother.

k) *Use in children:* Enalapril has not been studied in children.

Side Effect(s) / Adverse Reaction(s):
Enalapril has been demonstrated to be generally well tolerated. The overall incidence of side effects was no greater with enalapril than with placebo. For the most part, side effects have been mild and transient in nature, and have not required discontinuation of therapy. 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, diarrhea, muscle cramps, rash and cough. Less frequently renal dysfunction, renal failure and oliguria have been reported.

Drug Interactions:
a) *Antihypertensive Therapy:* Additive effects may occur when enalapril is used together with other antihypertensive.

b) *Serum Potassium:* If enalapril is given with potassium-losing diuretic, diuretic-induced hypokalemia may be ameliorated.
Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium containing salt substitutes.
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.
If concomitant use of previously-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

c) *Serum Lithium:* As with other drugs which eliminate sodium, lithium clearance may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be administrered.

d) *Nonsteroidal Anti-Inflammatory Drugs:* In some patients with compromised renal function who are being treated with nonsteroidal anti-inflammatory drugs, the co-administration of ACE inhibitors may result in a further deterioration of renal function. These effects are usually reversible.

Symptoms and Treatment for Overdosage, and Antidote(s):
Symptoms: Limited data are available for overdosage in humans. The most prominent features of overdosage reported to date are marked hypotension, beginning some 6 hrs after ingestion of tablets, concomitant with blockade 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 and 440mg of enalapril, respectively.
Treatment: The recommended treatment of overdosage is IV infusion of normal saline solution. If available, angiotensin II infusion may be beneficial. If ingestion is recent, induce emesis. Enalaprilat may be removed from the general circulation by hemodialysis.

Storage Condition(s):
Keep in a tight container. Store at temperature below 25°C. Protect from light and moisture.

Shelf-Life:
3 years from the date of manufacture.

Product Description and Packing(s):
Enapril tablet 10mg:
A brownish-red tablet, in the shape of " 

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Blister packing of 10's x 3, 10's x 10, 10's x 50 and 10's x 100.

Enapril tablet 20mg:
A light orange tablet, in the shape of " 

".
Blister packing of 10's x 3, 10's x 10, 10's x 50 and 10's x 100.

Y. S. P. ®
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