

## Enalapril Maleate

**Introduction:** Enalapril Maleate is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat.

**Mechanism of action:** Enalapril, after hydrolysis to enalaprilat, inhibits angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion.

### Pharmacology:

**Absorption:** Bioavailability is approximately 60%.  $T_{max}$  is within 1 h (enalapril); 3 to 4 h (enalaprilat).

**Distribution:** Enalapril crosses the blood-brain barrier poorly, if at all. Enalaprilat does not cross the blood-brain barrier.

**Metabolism:** Enalapril is a prodrug and is hydrolyzed to enalaprilat.

**Elimination:** Intact enalapril and approximately 40% of the dose as enalaprilat is excreted in the urine. Approximately 94% is recovered in the urine and feces.

**Renal Function Impairment:** In those with glomerular filtration rate 30 mL/min or less, the peak and trough enalaprilat levels increase,  $T_{max}$  increases, and time to steady state may be delayed.

Dosage adjustment recommended.

### Indications:

**Hypertension:** Enalapril maleate is indicated for the treatment of hypertension. Enalapril maleate is effective alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

**Heart Failure:** Enalapril maleate is indicated for the treatment of symptomatic congestive heart failure, usually in combination with diuretics and digitalis. In these patients enalapril maleate improves symptoms, increases survival, and decreases the frequency of hospitalization.

**Asymptomatic Left Ventricular Dysfunction:** In clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction <35 percent), enalapril maleate decreases the rate of development of overt heart failure and decreases the incidence of hospitalization for heart failure.

**Dosage:**

**Heart Failure: Adults:** PO Initial dose: 2.5 mg twice daily. Usual dose: 2.5 to 20 mg/day in 2 divided doses (max, 40 mg/day). The max daily dose is 40 mg in divided doses.

**High-Risk Patients: Adults:** IV Hypertensive patients at risk (eg, those with heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diureses or increase in diuretic dose, renal dialysis, or severe volume or salt depletion of any etiology) have potential for extremely hypotensive response. The starting dose should be 0.625 mg or less administered IV over a period of 5 min or more and preferably longer (up to 1 h).

**Hypertension: Adults:** PO Initial dose: 2.5 to 5 mg/day. Usual maintenance dose: 10 to 40 mg/day in single or twice daily doses. IV 1.25 mg over a 5-min period every 6 h. Dose may be repeated if after 1 h the clinical response is inadequate. Additional doses of 1.25 mg may be administered at 6-h intervals. For dialysis patients, the initial dose is 0.625 mg or less given over 5 min or preferably longer (up to 1 h).

**Children:** PO Initial dose: 0.08 mg/kg (up to 5 mg) every day. Adjust dose according to BP response. Doses above 0.58 mg/kg (or in excess of 40 mg) have not been studied in pediatric patients.

**Left Ventricular Dysfunction: Adults:** PO Initial dose: 2.5 mg twice daily.

**Renal Function Impairment: Adults:** Use an initial dosage of 5 mg/day in normal renal function and mild impairment (Ccr more than 30 mL/min); 2.5 mg/day in moderate to severe renal function impairment (Ccr 30 mL/min or less); and 2.5 mg on the day of dialysis in dialysis patients.

**Side effects: Cardiovascular:** Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients; pulmonary embolism and infarction; pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation; palpitation, Raynaud's phenomenon.

**Digestive:** Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, dyspepsia, constipation, glossitis, stomatitis, dry mouth.

**Hematologic:** Rare cases of neutropenia, thrombocytopenia and bone marrow depression.

**Musculoskeletal:** Muscle cramps.

**Nervous/Psychiatric:** Depression, confusion, ataxia, somnolence, insomnia, nervousness, peripheral neuropathy (e.g., paresthesia, dysesthesia), dream abnormality.

**Respiratory:** Bronchospasm, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection, pulmonary infiltrates, eosinophilic pneumonitis.

**Skin:** Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, pemphigus, herpes zoster, erythema multiforme, urticaria, pruritus, alopecia, flushing, diaphoresis, photosensitivity.

**Special Senses:** Blurred vision, taste alteration, anosmia, tinnitus, conjunctivitis, dry eyes, tearing.

**Urogenital:** Renal failure, oliguria, renal dysfunction, flank pain, gynecomastia, impotence.

**Precautions:**

**Hyperkalemia:** Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials.

In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8 percent of patients but was not a cause for discontinuation.

**Cough:** Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough

**Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril maleate may block 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.

**Nursing Mothers:** Enalapril maleate and enalaprilat have been detected in human breast milk. Because of the potential for serious adverse reactions in nursing infants from enalapril maleate, a decision should be made whether to discontinue nursing or to discontinue enalapril maleate, taking into account the importance of the drug to the mother.

**Pediatric Use:** Antihypertensive effects of enalapril have been established in hypertensive pediatric patients age 1 month to 16 years. Use of enalapril in these age groups is supported by evidence from adequate and well-controlled studies of enalapril in pediatric and adult patients as well as by published literature in pediatric patients.

**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.

**How supplied:** Customized as per request.