# CLINICAL UPDATE

| | |
|---|---|
| **Brand Name** | Enalapril maleate |
| **Generic Name** | enalapril maleate |
| **Drug Manufacturer** | Bionpharma Inc. |

## Clinical Update

### TYPE OF CLINICAL UPDATE

New Generic Dosage Form

### FDA APPROVAL DATE

August 10, 2021

### LAUNCH DATE

August 12, 2021

### REVIEW DESIGNATION

Standard

### TYPE OF REVIEW

Abbreviated New Drug Application (ANDA): 212408

### DISPENSING RESTRICTIONS

N/A

## Overview

### INDICATION(S) FOR USE

Enalapril is an angiotensin-converting enzyme inhibitor indicated for:

- treatment of symptomatic heart failure.
- treatment of asymptomatic left ventricular dysfunction, to decrease the rate of development of overt heart failure and reduce hospitalization for heart failure.

### MECHANISMS 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. The beneficial effects of enalapril in 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. Although the latter decrease is small, it results in small increases of serum potassium. In hypertensive patients treated with enalapril maleate tablets alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with enalapril maleate tablets plus a thiazide diuretic, there was essentially no change in serum potassium Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of enalapril remains to be elucidated.

## DOSAGE FORM(S) AND STRENGTH(S)

Enalapril maleate oral solution is a ready-to-use oral solution: 1 mg/mL enalapril maleate, USP.

## DOSE & ADMINISTRATION

Heart Failure: Initiate at 2.5 mg twice daily. Titrate up to 20 mg twice daily as tolerated.
Asymptomatic Left Ventricular Dysfunction: Initiate at 2.5 mg twice daily. Titrate up to 10 mg twice daily.
enalapril maleate oral solution is a ready-to-use solution intended for oral use only.

## EFFICACY

**Heart Failure, Mortality Trials**

In a multicenter, placebo-controlled clinical trial, 2,569 patients with all degrees of symptomatic heart failure and ejection fraction ≤35 percent were randomized to placebo or enalapril and followed for up to 55 months (SOLVD-Treatment). Use of enalapril was associated with an 11 percent reduction in all-cause mortality and a 30 percent reduction in hospitalization for heart failure. Diseases that excluded patients from enrollment in the study included severe stable angina (>2 attacks/day), hemodynamically significant valvular or outflow tract obstruction, renal failure (creatinine >2.5 mg/dL), cerebral vascular disease (e.g., significant carotid artery disease), advanced pulmonary disease, malignancies, active myocarditis and constrictive pericarditis. The mortality benefit associated with enalapril does not appear to depend upon digitalis being present.

The SOLVD-Prevention trial was not designed to determine whether treatment of asymptomatic patients with low ejection fraction would be superior, with respect to preventing hospitalization, to closer follow-up and use of enalapril at the earliest sign of heart failure. However, under the conditions of follow-up in the SOLVD-Prevention trial (every 4 months at the study clinic; personal physician as needed), 68% of patients on placebo who were hospitalized for heart failure had no prior symptoms recorded which would have signaled initiation of treatment.

The SOLVD-Prevention trial was also not designed to show whether enalapril modified the progression of underlying heart disease.

In another multicenter, placebo-controlled trial (CONSENSUS) limited to patients with NYHA Class IV congestive heart failure and radiographic evidence of cardiomegaly, use of enalapril was associated with improved survival. The results are shown in the following table.

| CONSENSUS Survival Rates | | |
|---|---|---|
| | SURVIVAL (%) | |
| | Six Months | One Year |
| VASOTEC (n = 127) | 74 | 64 |
| Placebo (n = 126) | 56 | 48 |

In both CONSENSUS and SOLVD-Treatment trials, patients were also usually receiving digitalis, diuretics, or both.