ENALAPRIL MALEATE - VASERETIC TABLETS (enalapril maleate, hydrochlorothiazide)

It is a white, or practically white, crystalline powder with a molecular weight of 386.32.

FORMULA

The formula is: C24H28Cl3N2O6S

Pharmacokinetics and Metabolism:

Enalaprilat is dialyzable at the rate of 62 mL/min. Studies in dogs indicate that enalapril crosses the blood-brain barrier poorly, if at all; enalaprilat does not enter the brain.

The disposition of enalapril and enalaprilat in patients with renal insufficiency is unknown. Based on urinary recovery, the extent of absorption of enalapril is approximately 94 percent of the dose is recovered in the urine and feces as enalaprilat or enalapril.

Enalapril is antihypertensive even in patients with low-renin hypertension. Although increased levels of bradykinin, a potent vasodepressor peptide, play a role in the mechanism of action of enalapril, there was essentially no change in serum potassium (see WARNINGS, POTASSIUM.

Mechanism of Action:

The mechanism of the antihypertensive effect of thiazides is unknown. The mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride ions in the urine. Various electrolytes including potassium, magnesium, and bicarbonate may be affected, although potassium depletion caused by thiazides is usually mild. The net effect on water and electrolyte balance is dependent upon the individual's fluid and electrolyte status, renal function, electrolyte concentrations, and administration of other drugs, especially mineralocorticoids.

The antihypertensive effect of diuretics is enhanced when they are used concomitantly with other antihypertensive agents such as beta-blockers, ACE inhibitors, calcium channel blockers, and angiotensin receptor blockers.

Drug Interactions

This fixed dose combination is not indicated for initial treatment (see DOSAGE AND ADMINISTRATION).

Achievement of optimal blood pressure reduction may require several weeks of treatment. The response to antihypertensive therapy is usually better in patients with moderately elevated blood pressures than in patients with severe hypertension. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of experiencing angioedema with enalapril. Patients with a history of angioedema resulting from ACE inhibitor therapy may develop angioedema with enalapril use in severely salt-depleted patients, including those who have concurrently received a diuretic.

Electrolyte disturbances may develop in patients with impaired renal function. Caution should be exercised whenever ACE inhibitors are administered to patients with impaired renal function. There is a risk of hyperkalemia in patients with renal insufficiency, diabetes, or Addison's disease. Monitoring serum potassium is particularly important when the patient is vomiting or receiving parenteral fluids.

In hemodynamic studies in patients with essential hypertension, blood pressure decreased more in the supine position than in the standing position. This may be of clinical importance in the elderly, in whom a greater degree of hypotension may occur in the standing position.

Enalapril should be discontinued and appropriate therapy and monitoring should be provided until normal blood pressure is reestablished.

Syncope has been reported in 1.3 percent of patients receiving VASERETIC. In two patients undergoing VASERETIC administration, syncope occurred in 1.3 percent of patients (see WARNINGS).

This drug combination should be used with caution in patients with a history of coronary artery disease, cerebrovascular disease, or peripheral vascular disease. Enalapril may accentuate myocardial ischemia by decreasing coronary blood flow and by decreasing cardiac contractility. Enalapril may be fatal.

ACE inhibitors may cause injury and death to the developing fetus. When pregnancy is confirmed, treatment should be discontinued. Cough:

Cough, a side effect of ACE inhibitors, has been shown to be frequency related and doserelated and to occur in patients classified with either mild, moderate, or severe hypertension. Cough may develop within hours or weeks of initiation of therapy or may occur after several months of continuous therapy. Cough develops in a greater proportion of patients receiving enalapril than captopril, which is also an ACE inhibitor. Available data from clinical trials of enalapril are insufficient to show that enalapril increases the risk of cough compared on a body surface area basis (mg/m²) to captopril.

Potassium:

Potassium determinations are particularly important when the patient is vomiting or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, dizziness,疲倦, muscular pain and cramps, and diarrhea.

Concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-rich diets with thiazide diuretics may cause hyperkalemia; use of potassium-sparing diuretics and/or potassium supplements is not recommended in patients receiving thiazide diuretics. Because of the potential fall in blood pressure in these patients, the administration of other drugs that lower blood pressure should be considered with caution.

ACE inhibitors may rarely produce angioedema, with or without accompanying dyspnea, which may be fatal. These complications occur more frequently in patients with renal impairment.

Cough associated with laryngeal edema is a potentially lethal complication. Angioedema associated with laryngeal edema may develop in patients with impaired renal function.

The antihypertensive effect may be augmented in patients with dietary sodium restriction and salt substitutes, which should be used cautiously, if at all, with enalapril.

This drug combination should be used with caution in patients with impaired renal function. In studies examining fetal abnormalities after exposure to antihypertensive use during pregnancy, hydrochlorothiazide was used at a rate equivalent to 4.7 mg/kg/day in rats and 30 mg/kg/day in mice. There was no teratogenicity in mice given up to 30 mg/kg/day or in rats given 30 mg/kg/day. No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits at doses up to 90 mg/kg/day and 10 mg/kg/day, respectively. Animal reproduction studies have not been conducted with the combination therapy. It is not known whether enalapril or hydrochlorothiazide can cause injury and even death to the developing fetus. Hence, VASERETIC is contraindicated in females who are or may become pregnant. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

The fetus is most sensitive to ACE inhibitors during the period of organ formation (second and third months of gestation). ACE inhibitors should be avoided during this period. After organ formation has occurred, ACE inhibitors may cause injury and death to the developing fetus. See WARNINGS: Fetal Toxicity.

Treatment of the newborn with diuretics may be required for several days after birth. Newborns of women treated with thiazides or their congeners should be monitored for hypoglycemia, hypokalemia, hyponatremia, and dehydration.

Monitoring of blood pressure and electrolyte determinations are particularly important when the patient is vomiting or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, dizziness, fatigue, lightheadedness, and/or confusion.

This drug combination has not been studied in patients with hepatic impairment. Caution should be exercised when using this drug combination in patients with hepatic impairment.

This drug combination has not been studied in patients with renal insufficiency. Caution should be exercised when using this drug combination in patients with renal insufficiency.

When VASERETIC is discontinued, the patient should be given substitute therapy to maintain adequate diuresis and blood pressure control.

The combination of enalapril and hydrochlorothiazide should be discontinued and appropriate therapy and monitoring should be provided until normal blood pressure is reestablished.

This drug combination should be used with caution in patients with a history of angioedema resulting from ACE inhibitor therapy. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of experiencing angioedema with enalapril use in severely salt-depleted patients, including those who have concurrently received a diuretic.
Patients should be cautioned to report lightheadedness especially if they have consulted with the prescribing physician.

Hypotension – Patients on Diuretic Therapy: To prevent postural hypotension, patients should be cautioned to rise slowly from a sitting or lying position. When oral hypoglycemics are used concomitantly with VASERETIC, caution should be exercised in selecting the dose and frequency of administration of the antidiabetic agent. In patients on VASERETIC and other agents that affect the RAS, in addition to decreases in blood pressure, hypokalemia may occur and there is an increased risk of hyperkalemia. Most patients receiving the combination of two RAS inhibitors do not obtain additional benefit with the combination and the incidence of side effects may be increased.

Hyperkalemia: Increases in cholesterol and triglyceride levels may be associated with thiazide diuretics. There is a rare possibility of hypercalcemia and hyperparathyroidism. Thiazides should be discontinued before carrying out tests for diagnosis of parathyroid adenoma.

Hyponatremia: May result in hypomagnesemia. Patients with diabetes mellitus may become manifest during thiazide therapy. May be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus in elderly patients may be either unmasked or may become manifest during thiazide therapy, and may be associated with hyperosmolar nonketotic coma or with rupture of a ketoacidotic state.

Placental Transfer: Drug concentrations in the cord blood of newborns of women taking VASERETIC were similar to those in the maternal plasma when maternal plasma concentrations were determined at delivery. The pharmacokinetics of enalapril and hydrochlorothiazide in nursing mothers have not been studied.

Consequences of Exposure to Drugs in Pregnancy: The consequences of exposure to VASERETIC during pregnancy. Discuss treatment options with patients. The information is intended to aid in the safe and effective use of VASERETIC and is not intended to be a substitute for proper medical care. A few cases of lithium toxicity have been reported in patients receiving combination therapy of lithium and VASERETIC. The daily dosage should not exceed two tablets of VASERETIC 10-25.

Inhibitors (COX-2 Inhibitors): These agents appear to inhibit RAS. This effect may be increased by antihypertensive agents that cause renin release (e.g., diuretics). Enalapril, which crosses the placenta, has been removed from neonatal milk. Enalapril maleate-hydrochlorothiazide is not recommended (see WARNINGS, PRECAUTIONS).

In a clinical pharmacology study, indomethacin or sulindac was administered to patients with hypertensive heart disease. After discontinuation of VASERETIC, there was a significant increase in blood pressure. This response is most likely due to the hypotensive effects of VASERETIC. The effect of VASERETIC on the pharmacokinetics of other drugs and the effect of other drugs on VASERETIC have not been studied. To prevent postural hypotension, patients should be advised to rise slowly and slowly from a sitting or lying position. When oral hypoglycemics are used concomitantly with VASERETIC, caution should be exercised in selecting the dose and frequency of administration of the antidiabetic agent.

DOSAGE AND ADMINISTRATION: The combination of enalapril and hydrochlorothiazide will be associated with both sets of contraindications. No specific information is available on the treatment of overdosage with enalapril and hydrochlorothiazide. When overdosage occurs, management should be symptomatic and supportive. The combination of enalapril and hydrochlorothiazide should be discontinued immediately and the patient observed, especially for cardiovascular and respiratory manifestations. Hypotension (systolic blood pressure less than 90 mm Hg) is the most frequent complaint in cases of enalapril overdose. Treatment of enalapril overdose usually requires careful observation for several days to ensure that hypotension does not recur when the drug has been excreted. Hemodialysis and peritoneal dialysis are not effective methods of removing enalapril from the circulation. Use the following dosage schedules when necessary:

- Enalapril Maleate: 2.5 mg either orally or subcutaneously every 1.5 hours until blood pressure is stabilized for at least an additional hour (see WARNINGS, PRECAUTIONS).
- Hydrochlorothiazide: 12.5 mg orally every 1.5 hours until blood pressure is stabilized for at least an additional hour (see WARNINGS, PRECAUTIONS).

In the presence of impaired renal function, lower starting doses of enalapril maleate and hydrochlorothiazide should be used (see PRECAUTIONS) and the patient observed carefully during the initial dosage adjustment period to determine the effective dosage for the patient. The following data are obtained from controlled trials: Cough: 1% of patients treated with VASERETIC reported the symptom at the time of occurrence of their first refill. This symptom was observed in 7% of the patients treated with placebo. This treatment-related symptom is apparently independent of dose; those of hydrochlorothiazide are a mixture of placebo- and enalapril-related events. The most frequent symptom was pharyngitis, with a reported incidence of 1.6% in patients treated with VASERETIC and 0.3% in patients treated with placebo. These events were mild to moderate and generally did not require discontinuation of therapy.

Inhibitors: The combination of enalapril and hydrochlorothiazide should be avoided in patients with asthma, angioneurotic edema, or a history of hypersensitivity reactions to ACE inhibitors. Enalapril, which crosses the placenta, has been removed from neonatal milk. Enalapril maleate-hydrochlorothiazide is not recommended (see WARNINGS, PRECAUTIONS).

Inhibitors (COX-2 Inhibitors): These agents appear to inhibit RAS. This effect may be increased by antihypertensive agents that cause renin release (e.g., diuretics). Enalapril, which crosses the placenta, has been removed from neonatal milk. Enalapril maleate-hydrochlorothiazide is not recommended (see WARNINGS, PRECAUTIONS).

In a clinical pharmacology study, indomethacin or sulindac was administered to patients with hypertensive heart disease. After discontinuation of VASERETIC, there was a significant increase in blood pressure. This response is most likely due to the hypotensive effects of VASERETIC. The effect of VASERETIC on the pharmacokinetics of other drugs and the effect of other drugs on VASERETIC have not been studied. To prevent postural hypotension, patients should be advised to rise slowly and slowly from a sitting or lying position. When oral hypoglycemics are used concomitantly with VASERETIC, caution should be exercised in selecting the dose and frequency of administration of the antidiabetic agent.

DOSAGE AND ADMINISTRATION: The combination of enalapril and hydrochlorothiazide will be associated with both sets of contraindications. No specific information is available on the treatment of overdosage with enalapril and hydrochlorothiazide. When overdosage occurs, management should be symptomatic and supportive. The combination of enalapril and hydrochlorothiazide should be discontinued immediately and the patient observed, especially for cardiovascular and respiratory manifestations. Hypotension (systolic blood pressure less than 90 mm Hg) is the most frequent complaint in cases of enalapril overdose. Treatment of enalapril overdose usually requires careful observation for several days to ensure that hypotension does not recur when the drug has been excreted. Hemodialysis and peritoneal dialysis are not effective methods of removing enalapril from the circulation. Use the following dosage schedules when necessary:

- Enalapril Maleate: 2.5 mg either orally or subcutaneously every 1.5 hours until blood pressure is stabilized for at least an additional hour (see WARNINGS, PRECAUTIONS).
- Hydrochlorothiazide: 12.5 mg orally every 1.5 hours until blood pressure is stabilized for at least an additional hour (see WARNINGS, PRECAUTIONS).

In the presence of impaired renal function, lower starting doses of enalapril maleate and hydrochlorothiazide should be used (see PRECAUTIONS) and the patient observed carefully during the initial dosage adjustment period to determine the effective dosage for the patient. The following data are obtained from controlled trials: Cough: 1% of patients treated with VASERETIC reported the symptom at the time of occurrence of their first refill. This symptom was observed in 7% of the patients treated with placebo. This treatment-related symptom is apparently independent of dose; those of hydrochlorothiazide are a mixture of placebo- and enalapril-related events. The most frequent symptom was pharyngitis, with a reported incidence of 1.6% in patients treated with VASERETIC and 0.3% in patients treated with placebo. These events were mild to moderate and generally did not require discontinuation of therapy.

Inhibitors: The combination of enalapril and hydrochlorothiazide should be avoided in patients with asthma, angioneurotic edema, or a history of hypersensitivity reactions to ACE inhibitors. Enalapril, which crosses the placenta, has been removed from neonatal milk. Enalapril maleate-hydrochlorothiazide is not recommended (see WARNINGS, PRECAUTIONS).

In a clinical pharmacology study, indomethacin or sulindac was administered to patients with hypertensive heart disease. After discontinuation of VASERETIC, there was a significant increase in blood pressure. This response is most likely due to the hypotensive effects of VASERETIC. The effect of VASERETIC on the pharmacokinetics of other drugs and the effect of other drugs on VASERETIC have not been studied. To prevent postural hypotension, patients should be advised to rise slowly and slowly from a sitting or lying position. When oral hypoglycemics are used concomitantly with VASERETIC, caution should be exercised in selecting the dose and frequency of administration of the antidiabetic agent.