

Zepres Plus

(Enalapril Maleate U.S.P.+Hydrochlorothiazide B.P.)

(الیناپریل میلیٹھ یو ایس پی + ہائیڈروکلورو تھائیائیڈ بی پی)

زی پریس پلس

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, **Zepres Plus** should be discontinued as soon as possible.

COMPOSITION

Each **Zepres Plus** tablet contains 10 mg of Enalapril Maleate and 25 mg of Hydrochlorothiazide. "Product contains Lactose"

CLINICAL PHARMACOLOGY

Mechanism of Action

Zepres Plus provides anti-hypertensive and diuretic activity. Enalapril Maleate and Hydrochlorothiazide have been used singly and concomitantly for the treatment of hypertension. The anti-hypertensive effects of these two agents are additive and are sustained for at least 24 hours.

Enalapril Maleate

Enalapril, after hydrolysis to enalaprilat, inhibits angiotensin-converting enzyme (ACE). The mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system. 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. In patients treated with Enalapril Maleate plus a thiazide diuretic, there was essentially no change in serum potassium.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate.

PHARMACOKINETICS

Enalapril Maleate

Absorption: Following oral administration of Enalapril Maleate, peak serum concentrations of Enalapril occur within about one hour. The extent of absorption of enalapril is approximately 60%. Enalapril absorption is not influenced by the presence of food in the gastrointestinal tract.

Metabolism: Following absorption, enalapril is hydrolyzed to enalaprilat, which is a more potent angiotensin converting enzyme inhibitor than enalapril.

Distribution: Peak serum concentrations of enalaprilat occur three to four hours after an oral dose of Enalapril Maleate. **Excretion:** Excretion of enalaprilat and enalapril is primarily renal. Approximately 94% of the dose is recovered in the urine and feces as enalaprilat or enalapril. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril.

PHARMACODYNAMICS

In most patients studied, after oral administration of a single dose of Enalapril Maleate, onset of antihypertensive activity was seen at one hour with peak reduction of blood pressure achieved by four to six hours. At recommended doses, antihypertensive effects of Enalapril Maleate monotherapy have been maintained for at least 24 hours. In some patients the effects may diminish toward the end of the dosing interval; this was less frequently observed with concomitant administration of Enalapril Maleate and Hydrochlorothiazide. Achievement of optimal blood pressure reduction may require several weeks of enalapril therapy in some patients. The antihypertensive effects of enalapril have continued during long-term therapy. Abrupt withdrawal of enalapril has not been associated with a rapid increase in blood pressure.

Hydrochlorothiazide

After oral use diuresis begins within two hours, peaks in about four hours and lasts about 6 to 12 hours. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

Distribution: Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

Metabolism and Elimination: Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

INDICATIONS

Zepres Plus is indicated for the treatment of hypertension.

This fixed dose combination is not indicated for initial treatment.

DOSEAGE AND ADMINISTRATION

A patient whose blood pressure is not adequately controlled with either enalapril or Hydrochlorothiazide monotherapy may be given **Zepres Plus**. Further increases of enalapril, Hydrochlorothiazide or both depend on clinical response. The Hydrochlorothiazide dose should generally not be increased until 2-3 weeks have elapsed. In general, patients do not require doses in excess of 20 mg of enalapril or 50 mg of Hydrochlorothiazide. The daily dosage should not exceed two tablets of **Zepres Plus**.

Use in Renal Impairment: The usual regimens of therapy with **Zepres Plus** need not be adjusted as long as the patient's creatinine clearance is $> 30 \text{ mL/min/1.73m}^2$ (serum creatinine approximately $\leq 3 \text{ mg/dL}$ or $265 \mu\text{mol/L}$). In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Enalapril Maleate-Hydrochlorothiazide is not recommended.

SIDE EFFECTS

In clinical trials with **Zepres Plus** no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with enalapril or Hydrochlorothiazide. The most frequent clinical adverse experiences in controlled trials were: dizziness (6.5%), headache (5.5%), fatigue (3.9%) and cough (3.5%). Generally, adverse experiences were mild and transient in nature. Adverse experiences occurring in greater than two percent of patients treated with **Zepres Plus** in controlled clinical trials are muscle cramps, nausea, asthenia, orthostatic effects, impotence, and diarrhea.

Clinical adverse experiences occurring in 0.5 to 2.0% of patients in controlled trials included:

Body As A Whole: Syncope, chest pain, abdominal pain.

Cardiovascular: Orthostatic hypotension, palpitation, tachycardia.

Digestive: Vomiting, dyspepsia, constipation, flatulence, dry mouth.

Nervous/Psychiatric: Insomnia, nervousness, paresthesia, somnolence, vertigo.

Skin: Pruritus, rash.

Other: Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection. Angioedema: Angioedema has been reported in patients receiving **Zepres Plus**, with an incidence higher in black than in non-black patients. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with **Zepres Plus** should be discontinued and appropriate therapy instituted immediately. Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9%), orthostatic hypotension (1.5%), other orthostatic effects (2.3%). In addition syncope occurred in 1.3% of patients.

Clinical Laboratory Test Findings

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine were observed in about 0.6% of patients. Increases are more likely to occur in patients with renal artery stenosis.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit occur frequently in hypertensive patients treated with **Zepres Plus** but are rarely of clinical importance unless another cause of anemia coexists.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

DRUG INTERACTIONS

Enalapril Maleate

Hypotension: 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 minimized 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 medical supervision for at least two hours and until blood pressure has stabilized 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).

NSAIDs: In some patients with compromised renal function who are being treated with NSAIDs, the coadministration of enalapril may result in a further deterioration of renal function. These effects are usually reversible. NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors. Other Cardiovascular Agents: Enalapril has been used concomitantly with beta-blockers, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: Enalapril attenuates diuretic-induced potassium loss. 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 hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Gold: Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomate) and concomitant ACE inhibitor therapy including **Zepres Plus**.

Hydrochlorothiazide

When administered concurrently the following drugs may interact with thiazide diuretics: Alcohol, barbiturates, or narcotics - potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs: Additive effect or potentiation.

Cholestyramine and colestipol resins: Absorption of Hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the Hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use. Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant. Lithium: Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with **Zepres Plus**. NSAIDs: In some patients, the administration of a NSAID can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when **Zepres Plus** and NSAIDs are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

WARNINGS

General

Enalapril Maleate

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis. The incidence of syncope may be reduced by proper titration of the individual components.

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Anaphylactoid and Possibly Related Reactions: Presumably because ACE inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors may be subject to a variety of adverse reactions, some of them are serious.

Head and Neck Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx may occur at any time during treatment. In such cases **Zepres Plus** should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred.

Intestinal Angioedema: These patients presented with abdominal pain (with or without nausea or vomiting). Anaphylactoid reactions during desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions.

Anaphylactoid reactions during membrane exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered. **Hepatic Failure:** Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Pregnancy: Pregnancy Categories C (first trimester) and D (second and third trimesters). When pregnancy is detected, **Zepres Plus** should be discontinued as soon as possible.

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

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

PRECAUTIONS

General

Enalapril Maleate

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.

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. In such patients renal function should be monitored during the first few weeks of therapy. Some patients with hypertension or heart failure with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hyperkalemia: Hyperkalemia was less frequent (approximately 0.1%) in patients treated with enalapril plus Hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril.

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 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.

Hydrochlorothiazide

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss.

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

OVERDOSE

Treatment is symptomatic and supportive. Therapy with **Zepres Plus** should be discontinued and the patient observed closely. Suggested measures include induction of emesis and/or gastric lavage, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

Enalaprilat may be removed from general circulation by hemodialysis and has been removed from neonatal circulation by peritoneal dialysis.

CONTRAINDICATIONS

Zepres Plus is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor and in patients with hereditary or idiopathic angioedema. Because of the Hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

PRESENTATION

Zepres Plus tablet: 2x10's/pack

Dosage:

As directed by the physician.

Instructions:

Store below 30°C.

Protect from sunlight & moisture.

Keep out of reach of children.

Detailed prescribing information is available on request.



Manufactured by:
AsianContinental (Pvt.) Ltd.
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Karachi-Pakistan.



An ISO Certified Company

LFT/032/02

خوراک:
ڈائٹریکی ہدایت کے مطابق استعمال کریں۔
ہدایتات:
دوا کو 30 ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔