

Zepres

(Enalapril Maleate)

زیپریس

Each **Zepres** 5mg tablet contains 5mg of enalapril maleate.
Each **Zepres** 10mg tablet contains 10mg of enalapril maleate.

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 hypertension and 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. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. While the mechanism through which **Zepres** lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, **Zepres** is antihypertensive even in patients with low-renin hypertension.

Absorption: Oral enalapril is rapidly absorbed. The extent of absorption of enalapril from oral enalapril tablet is approximately 60%. The absorption of **Zepres** is not influenced by the presence of food in the gastrointestinal tract. Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur about 4 hours after an oral dose of enalapril tablet. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril is 11 hours.

Elimination: Excretion of enalaprilat is primarily renal. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril (about 20%).

Renal impairment: The exposure of enalapril and enalaprilat is increased in patients with renal insufficiency. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency and time to steady state is delayed. Enalaprilat may be removed from the general circulation by hemodialysis.

Hypertension: Zepres is effective alone or in combination with other antihypertensive agents, especially thiazide-type diuretics. **Heart Failure:** Zepres is indicated for the treatment of symptomatic congestive heart failure, usually in combination with diuretics and digitalis.

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of **Zepres**. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with **Zepres** to reduce the likelihood of hypotension. If the patient's blood pressure is not controlled with **Zepres** alone, diuretic therapy may be resumed. If the diuretic cannot be discontinued an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour.

The recommended initial dose in patients not on diuretics is 5 mg once a day. The usual dosage range is 10 to 40 mg per day administered in a single dose or two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. If blood pressure is not controlled with **Zepres** alone, a diuretic may be added.

The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Renal Status	Creatinine-Clearance mL/min	Initial Dose mg/day
Normal Renal Function	>80 mL/min	5 mg
Mild Impairment	≤ 80 >30 mL/min	5 mg
Moderate to Severe Impairment	≤ 30 mL/min	2.5 mg
Dialysis Patients*	-	2.5 mg on dialysis days†

†Dosage on nondialysis days should be adjusted depending on the blood pressure response.

Zepres is indicated for the treatment of symptomatic heart failure, usually in combination with diuretics and digitalis. The recommended initial dose is 2.5 mg. The recommended dosing range is 2.5 to 20 mg given twice a day. Doses should be titrated upward, as tolerated, over a period of a few days or weeks. The maximum daily dose administered in clinical trials was 40 mg in divided doses. After the initial dose of **Zepres**, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. If possible, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of **Zepres** does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

After the initial dose of **Zepres**, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. If possible, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of **Zepres** does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

In patients with heart failure who have hyponatremia (serum sodium less than 130 mEq/L) or with serum creatinine greater than 1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

Antihypertensive effects of **Zepres** have been established in hypertensive pediatric patients age 1 month to 16 years. The usual recommended starting dose is 0.08 mg/kg (up to 5 mg) once daily. Dosage should be adjusted according to blood pressure response. Doses above 0.58 mg/kg (or in excess of 40 mg) have not been studied in pediatric patients.

Blood and the lymphatic system disorders: Anaemia (including aplastic and hemolytic), neutropenia, decrease in hemoglobin, decrease in hematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, lymphadenopathy and autoimmune diseases.

Endocrine disorders: Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Nervous system and psychiatric disorders: Headache, depression, confusion, somnolence, insomnia, nervousness, paresthaesia, vertigo, dream abnormality and sleep disorders.

Eye disorders: Blurred vision.

angina pectoris, tachycardia, orthostatic hypotension, palpitation, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients and Raynaud's phenomenon.

Respiratory, thoracic and mediastinal disorders: Cough, dyspnea, rhinorrhea, sore throat and hoarseness, bronchospasm/asthma, pulmonary infiltrates, rhinitis and allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorders: Nausea, diarrhoea, abdominal pain, taste alteration, ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritation, dry mouth, peptic ulcer, stomatitis/aphthous ulceration, glossitis and intestinal angioedema.
Hepatobiliary disorders: Hepatic failure, hepatitis - either hepatocellular or cholestatic, hepatitis including necrosis & cholestasis (including jaundice).

Skin and subcutaneous tissue disorders: Rash, hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported, diaphoresis, pruritus, urticaria, alopecia, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, pemphigus and erythroderma. A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

Renal and urinary disorders: Renal dysfunction, renal failure, proteinuria and oliguria.

Reproductive system and breast disorders: Impotence and gynecomastia.

General disorders and administration site conditions: Asthenia, fatigue, muscle cramps, flushing, tinnitus, malaise and fever. **Investigations:** Hyperkalemia, increase in serum creatinine, increase in blood urea, hyponatremia, elevations of liver enzymes and elevations of serum bilirubin. Incidence rates were comparable to those in the placebo and active control groups in the clinical trials.

DRUG INTERACTIONS

Hypotension - Patients on Diuretic Therapy: 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 close medical supervision after the initial dose 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 **Zepres** is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Non-steroidal Anti-inflammatory Agents: In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration 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: **Zepres** has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, prazosin and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: **Zepres** attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretic (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. Potassium sparing agents should generally not be used in patients with heart failure receiving **Zepres**.

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 aurothiomalate) and concomitant ACE inhibitor therapy including **Zepres**.

WARNINGS

Anaphylactoid and Possibly Related Reactions: Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including **Zepres**) may be subject to a variety of adverse reactions, some of them serious.

Head and Neck Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including **Zepres**. This may occur at any time during treatment. In such cases **Zepres** 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: Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor.

Anaphylactoid reactions during desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

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.

Hypotension: Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology.

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme 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. Marketing experience has revealed cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hepatic Failure: Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis, and (sometimes) death. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS

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: In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including **Zepres**, 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 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. 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 increase in blood urea and serum creatinine, usually minor and transient, especially when **Zepres** has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or **Zepres** may be required. Evaluation of patients with hypertension or heart failure should always include assessment of renal function.

Hyperkalemia: 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 **Zepres**.

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.

Pregnancy: Pregnancy Categories C (first trimester) and D (second and third trimesters)

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

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

Pediatric Use: **Zepres** is not recommended in neonates and in pediatric patients with glomerular filtration rate < 30 mL/min/1.73 m2, as no data are available.

OVERDOSE

The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution.

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

CONTRAINDICATIONS

Zepres 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.

PRESENTATION

Zepres tablet 5mg: 2x10's/pack

Zepres tablet 10mg: 2x10's/pack

Issued: 10/2011

خوراک:
ڈاکٹر کی ہدایت کے مطابق۔
ہدایات:
دوا کو ہم ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔

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LFT/007/01