APPROVED

Order of Ministry

of Health of Ukraine

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Marketing Authorization

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**AMENDED**

**Order of Ministry of Health**

**of Ukraine No. 382**

**of 25.06.2015**

INSTRUCTION

for medical use of medicinal product

ENALOZID® MONO

Composition:

Active ingredient: enalapril;

1 tablet containing enalapril maleate on a 100% substance basis 5 mg or 10 mg;

Excipients: lactose monohydrate, corn starch, povidone, calcium stearate.

Pharmaceutical form

Tablets.

Basic physical and chemical properties: White to off-white, flat-faced, bevelled-edged, scored or non-scored tablets.

Pharmacotherapeutic group

Angiotensin-converting enzyme inhibitors, plain. АТС Code С09А А02.

Pharmacological properties

Pharmacodynamics

Enalozid® Mono (enalapril maleate) is the maleate salt of enalapril, a derivative of two amino-acids, L-alanine and L-proline.

Mechanism of action

Angiotensin converting enzyme is a peptidyl dipeptidase which catalyses the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, enalapril is hydrolysed to enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreased aldosterone secretion.

ACE is identical to kininase II. Thus enalapril maleate may also block the degradation of bradykinin, a potent vasodepressor peptide.

While the mechanism through which enalapril maleate lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, enalapril maleate is antihypertensive even in patients with low-renin hypertension. Administration of enalapril maleate to patients with hypertension results in a reduction of both supine and standing blood pressure without a significant increase in heart rate.

Symptomatic postural hypotension is infrequent. In some patients the development of optimal blood pressure reduction may require several weeks of therapy. Abrupt withdrawal of enalapril maleate has not been associated with rapid increase in blood pressure. Effective inhibition of ACE activity usually occurs 2 to 4 hours after oral administration of an individual dose of enalapril. Onset of antihypertensive activity was usually seen at one hour, with peak reduction of blood pressure achieved by 4 to 6 hours after administration. The duration of effect is dose-related. However, at recommended doses, antihypertensive and haemodynamic effects have been shown to be maintained for at least 24 hours.

In haemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of enalapril maleate there was an increase in renal blood flow; glomerular filtration rate was unchanged. There was no evidence of sodium or water retention. However, in patients with low pre-treatment glomerular filtration rates, the rates were usually increased.

In studies in diabetic and non-diabetic patients with renal disease, decreases in albuminuria and urinary excretion of IgG and total urinary protein were seen after the administration of enalapril.

When given together with thiazide-type diuretics, the blood pressure-lowering effects of enalapril maleate are at least additive. Enalapril maleate may reduce or prevent the development of thiazide-induced hypokalaemia.

In patients with heart failure on therapy with digitalis and diuretics, treatment with oral or injection enalapril maleate was associated with decreases in peripheral resistance and blood pressure. Cardiac output increased, while heart rate (usually elevated in patients with heart failure) decreased. Pulmonary capillary wedge pressure was also reduced. Exercise tolerance and severity of heart failure, as measured by New York Heart Association criteria, improved. These actions continued during chronic therapy.

In patients with mild to moderate heart failure, enalapril retarded progressive cardiac dilatation/enlargement and failure, as evidenced by reduced left ventricular end diastolic and systolic volumes and improved ejection fraction.

Pharmacokinetics

Absorption

Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril tablet is approximately 60%. The absorption of oral enalapril is not influenced by the presence of food in the gastro-intestinal 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 enalapril following multiple doses of oral enalapril is 11 hours. In subjects with normal renal function, steady-state serum concentrations of enalaprilat were reached after 4 days of treatment.

Distribution

Over the range of concentrations which are therapeutically relevant, enalaprilat binding to human plasma proteins does not exceed 60 %.

Biotransformation

Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril.

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. In patients with mild to moderate renal insufficiency (creatinine clearance 40-60 mL/min) steady state AUC of enalaprilat was approximately two-fold higher than in patients with normal renal function after administration of 5 mg once daily. In severe renal impairment (creatinine clearance ≤ 30 mL/min), AUC was increased approximately 8-fold. The effective half-life of enalaprilat is prolonged at this level of renal insufficiency and time to steady state is delayed.

Enalaprilat may be removed from the general circulation by haemodialysis. The dialysis clearance of enalaprilat is 62 mL/min.

Clinical particulars

Indications

* Treatment of hypertension.
* Treatment of severe heart failure.
* Prevention of symptomatic heart failure in patients with asymptomatic left ventricular dysfunction (ejection fraction ≤ 35%).

Contraindications

* Hypersensitivity to enalapril, to any of the excipients or any other ACE inhibitor.
* History of angioedema associated with previous ACE-inhibitor therapy.
* Hereditary or idiopathic angioedema.
* Pregnant women or women who are planning pregnancy (see section “Pregnancy and lactation”).

The concomitant use of Enalozid® Mono with aliskiren–containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m2).

Interaction with other medicinal products and other forms of interaction

Hypotension therapy

Concomitant use of these agents may increase the hypotensive effects of enalapril. Concomitant use with nitroglycerine and other nitrates, or other vasodilators, may further reduce blood pressure.

Potassium-sparing diuretics or potassium supplements

ACE inhibitors attenuate diuretic-induced potassium loss. Potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium (see Section “*Special warnings and precautions for use”*).

Diuretics (thiazide or loop diuretics)

Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with enalapril (see Section “*Special warnings and precautions for use”*). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of enalapril.

Antidiabetic drugs

Concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose- lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment (see Sections “*Special warnings and precautions for use”, “Undesirable effects”*).

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors. Use of enalapril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see Section “*Special warnings and precautions for use”*).

*Tricyclic Antidepressants/Antipsychotics/Anaesthetics/Hypnotics*

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see Section “*Special warnings and precautions for use”*).

Non-steroidal anti-inflammatory drugs including selective cyclooxygenase-2 inhibitors.

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 (COX-2) inhibitors may reduce the effect of diuretics and other antihypertensive drugs. Therefore, the antihypertensive effect of angiotensin II receptor antagonists, ACE inhibitors or diuretics may be attenuated by NSAIDs including selective COX-2 inhibitors.

The co-administration of NSAIDs (including COX-2 inhibitors) and angiotensin II receptor antagonists or ACE inhibitors exert an additive effect on the increase in serum potassium, and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function (such as the elderly or patients who are volume-depleted, including those on diuretic therapy). Therefore, the combination should be administered with caution in patients with compromised renal function. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

Dual blockade of the renin-angiotensin-aldosterone system

Dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through angiotensin receptor blockers, ACE inhibitors or direct renin inhibitors (e.g. aliskiren) is associated with a higher risk of hypotension, syncope, hyperkalaemia, and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent. Close monitoring of blood pressure, renal function and electrolytes should be used in patients receiving enalapril and other drugs affecting RAAS. The concomitant use of enalapril with aliskiren is contraindicated in patients with diabetes mellitus. The concomitant use of enalapril with aliskiren is contraindicated in patients with renal impairment (glomerular filtration rate < 60 mL/min).

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including enalapril.

*Sympathomimetics*

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Alcohol

Alcohol enhances the hypotensive effect of ACE inhibitors.

*Acetyl salicylic acid, thrombolytics and β-blockers*

Enalapril can be safely administered concomitantly with acetyl salicylic acid (at cardiologic doses), thrombolytics and β-blockers.

Concomitant therapy with an ACE inhibitor and an angiotensin receptor antagonist

It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, concomitant therapy with ACE inhibitor and angiotensin-receptor blocker is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and worsening renal function (including acute renal failure) as compared to use of a single angiotensin receptor agent. Dual blockade (e.g, by combining an ACE-inhibitor with an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function, potassium levels, and blood pressure.

Special warnings and precautions for use

Symptomatic hypotension

Symptomatic hypotension is seen in uncomplicated hypertensive patients. In hypertensive patients receiving enalapril, symptomatic hypotension is more likely to occur if the patient has been volume depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting (see Sections “*Interaction with other medicinal products and other forms of interaction”* and “*Undesirable effects”*). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In these patients, enalapril therapy should be started under medical supervision. The patients should be followed closely whenever the dose of enalapril and/or diuretic is adjusted. Similar considerations may apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion. In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with enalapril. This effect is anticipated, and usually is not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or Enalozid® Mono may be necessary.

Aortic or mitral valve stenosis/hypertrophic cardiomyopathy

As with all vasodilators, ACE inhibitors should be given with caution to patients with left ventricular valvular outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Renal impairment

In cases of renal impairment (creatinine clearance <80 mL/min) the initial enalapril dosage should be adjusted according to the patient's creatinine clearance (see Section “*Posology and method of administration”*) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients. Renal failure has been reported in association with enalapril and has been mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognised promptly and treated appropriately, renal failure when associated with therapy with enalapril is usually reversible.

Some hypertensive patients with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when enalapril has been given concurrently with a diuretic. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying renal artery stenosis (see Section *“Special warnings and precautions for use”*).

Renovascular hypertension

There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Loss of renal function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under close medical supervision with low doses, careful titration, and monitoring of renal function.

Kidney transplantation

There is no experience regarding the administration of enalapril in patients with a recent kidney transplantation. Treatment with Enalozid® Mono is therefore not recommended.

Hepatic insufficiency

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Neutropenia/Agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Enalapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If enalapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Hypersensitivity/Angioneurotic oedema

Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. In such cases, enalapril should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. In cases where the swelling is localized in the tongue, glottis or larynx, especially in patients with the history of respiratory surgery airway obstruction can develop. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy which may include subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures to ensure a patent airway, should be administered promptly.

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.

Patients with a history of angiooedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see Section “Contraindications”).

Anaphylactoid reactions during hymenoptera desensitisation

Rarely, patients receiving ACE inhibitors during desensitisation with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each desensitisation.

Anaphylactoid reactions during low density lipoprotein apheresis

Rarely, patients receiving ACE inhibitors during low density lipoprotein apheresis with dextran sulphate have experienced life-threatening anaphylactic reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

Haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE inhibitor. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hypoglycaemia

Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor should be told to closely monitor for hypoglycaemia, especially during the first month of combined use (see Section “*Interaction with other medicinal products and other forms of interaction”*).

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent, and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, enalapril blocks 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.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including enalapril. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of enalapril and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see Section “*Interaction with other medicinal products and other forms of interaction”*).

Lithium

The combination of lithium and enalapril is generally not recommended (see Section “Interaction with other medicinal products and other forms of interaction”).

Concomitant therapy with an ACE inhibitor and an angiotensin receptor antagonist

Combining an ACE-inhibitor with an angiotensin II receptor antagonist should be limited to individually defined cases with close monitoring of renal function, potassium levels, and blood pressure (see Section “Interaction with other medicinal products and other forms of interaction”).

Lactose

Enalozid® Mono contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Pregnancy and lactation

Pregnancy

Enalozid® Mono is contraindicated in pregnant women or those planning pregnancy. When pregnancy is diagnosed, treatment with the drug should be stopped immediately, and, if appropriate, alternative therapy with an established safety profile for use in pregnancy should be started.

Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.  Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension

Lactation.

Limited pharmacokinetic data demonstrate very low concentrations in breast milk. Although these concentrations seem to be clinically irrelevant, the use of Enalozid® Mono in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In the case of an older infant, the use of Enalozid® Mono in a breastfeeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

Effects on speed of reactions when driving or using machinery

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

Posology and method of administration

The absorption of Enalozid® Mono is not affected by food. The tablet is not divided. If the drug is prescribed in doses less than 5 mg, the appropriate enalapril products with such a dosage should be used.

The dose should be individualised according to patient profile (see Section “*Special warnings and precautions for use”*) and blood pressure response.

Hypertension.

The initial dose is 5 to maximally 20 mg, depending on the degree of hypertension and the condition of the patient (see below). Enalozid® Mono is given once daily. In mild hypertension, the recommended initial dose is 5 to 10 mg.

Patients with a strongly activated renin-angiotensin-aldosterone system, (e.g., renovascular hypertension, salt and/or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A starting dose of 5 mg or lower is recommended in such patients and the initiation of treatment should take place under medical supervision.

Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with enalapril. A starting dose of 5 mg or lower is recommended in such patients. If possible, diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Enalozid® Mono. Renal function and serum potassium should be monitored.

The usual maintenance dose is 20 mg daily. The maximum maintenance dose is 40 mg daily.

*Heart failure/Asymptomatic left ventricular dysfunction*

In the management of symptomatic heart failure, Enalozid® Mono is used in addition to diuretics and, where appropriate, digitalis or beta-blockers. The initial dose of Enalozid® Mono in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2.5 mg, and it should be administered under close medical supervision to determine the initial effect on the blood pressure. In the absence of, or after effective management of, symptomatic hypotension following initiation of therapy with enalapril in heart failure, the dose should be increased gradually to the usual maintenance dose of 20 mg, given in a single dose or two divided doses, as tolerated by the patient. This dose titration is recommended to be performed over a 2 to 4 week period. Such therapeutic regimen effectively reduces the mortality rates of patients with clinical heart failure. The maximum dose is 40 mg daily given in two divided doses.

Suggested dosage titration of Enalozid® Mono in patients with heart failure/asymptomatic left ventricular dysfunction

|  |  |
| --- | --- |
| Week | Dose, mg/day |
| Week 1 | Days 1 to 3: 2.5 mg/day\* in a single dose  Days 4 to 7: 5 mg/day in two divided doses |
| Week 2 | 10 mg/day in a single dose or in two divided doses |
| Weeks 3 and 4 | 20 mg/day in a single dose or in two divided doses |

\*Special precautions should be followed in patients with impaired renal function or taking diuretics (see Section “*Special warnings and precautions for use”*).

Blood pressure and renal function should be monitored closely both before and after starting treatment with Enalozid® Mono (see Section “*Special warnings and precautions for use”*) because hypotension and (more rarely) consequent renal failure have been reported. In patients treated with diuretics, the dose should be reduced if possible before beginning treatment with Enalozid® Mono. The appearance of hypotension after the initial dose of Enalozid® Mono does not imply that hypotension will recur during chronic therapy with enalapril and does not preclude continued use of the drug. Renal function and serum potassium should be monitored.

*Dosage in renal insufficiency*

Generally, the intervals between the administrations of enalapril should be prolonged and/or the dosage reduced.

|  |  |  |
| --- | --- | --- |
| Renal status | Creatinine clearance (CrCL), mL/min | Initial dose mg/day |
| Mild renal failure | 30<CrCL<80 | 5-10 mg |
| Moderate renal failure | 10<CrCL≤30 | 2.5 mg |
| Severe impairment. Usually these patients are on hemodialysis. | CrCL≤10 | 2.5 mg in days of dialysis\* |

\* See Section “Special warnings and precautions for use”: *Haemodialysis patients.*

Enalapril is dialysable. Dosage on nondialysis days should be adjusted depending on the blood pressure response.

*Use in elderly*

The dose should be in line with the renal function of the elderly patient (See Section “Special warnings and precautions for use”).

*Children with hypertension above 6 years of age*

There is limited clinical trial experience of the use of Enalapril in hypertensive paediatric patients. For patients who can swallow tablets, the dose should be individualised according to patient profile and blood pressure response. The recommended initial dose is 2.5 mg in patients 20 to 50 kg and 5 mg in patients ≥50 kg. Enalozid® Mono is given once daily. The dosage should be adjusted according to the needs of the patient to a maximum of 20 mg daily in patients 20 to 50 kg and 40 mg in patients ≥50 kg.

Enalozid® Mono is not recommended in neonates and in paediatric patients with glomerular filtration rate <30 mL/min/1.73 m2, as no data are available.

Children

The product is used in children above 6 years.

Enalozid® Mono is not recommended in neonates and in paediatric patients with glomerular filtration rate <30 mL/min/1.73 m2, as no data are available.

Overdose

Limited data are available for overdosage in humans. The most prominent features of overdosage reported to date are marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor. Symptoms associated with overdosage of ACE inhibitors may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. Serum enalaprilat levels 300- and 440-fold higher than usually seen after therapeutic doses have been reported after ingestion of 100 mg and 200 mg of enalapril, respectively.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating enalapril maleate (e.g., emesis, gastric lavage, administration of absorbents, and sodium sulphate). Enalaprilat may be removed from the general circulation by haemodialysis (see Section “*Special warnings and precautions for use*. Haemodialysis patients”). Pacemaker therapy is indicated for therapy - resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

Undesirable effects

Blood and lymphatic system disorders: Anaemia (including aplastic and haemolytic), neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, lymphadenopathy, autoimmune diseases.

Endocrine system disorders: syndrome of inappropriate antidiuretic hormone secretion.

Metabolism and nutrition disorders: hypoglycaemia.

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

Eye disorders: blurred vision.

Cardiac and vascular system disorders: dizziness, hypotension (including orthostatic hypotension), syncope, chest pain, rhythm disturbances, angina pectoris, tachycardia; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see Section “*Special warnings and precautions for use”*); Raynaud's phenomenon.

Respiratory disorders: cough, dyspnea, rhinorrhoea, sore throat and hoarseness, bronchospasm/asthma, pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorders: nausea, diarrhoea, abdominal pain, taste alteration, ileus, pancreatitis, peptic ulcer, vomiting, dyspepsia, constipation, anorexia, gastric irritations, dry mouth, stomatitis/aphthous ulcerations, glossitis, 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 (face, extremities, lips, tongue, glottis and/or larynx), diaphoresis, pruritus, urticaria, alopecia, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, pemphigus, erythroderma.

A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, positive antinuclear antibodies (ANA), elevated erythrocyte sedimentation rate (ESR), eosinophilia, and leucocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

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

Reproductive system and breast disorders: impotence, gynecomastia.

General disorders and administration site conditions: asthenia, fatigue, muscle cramps, flushing, tinnitus, malaise, fever.

*Investigations:* hyperkalaemia, increases in serum creatinine, increases in blood urea, hyponatraemia, elevations of liver enzymes, elevations of serum bilirubin.

Shelf life

3 years.

Do not use this medicine after the expiry date stated on the carton.

Storage

Store in the original package. Store below 25 °С. Keep out of the reach of children.

Nature and contents of container

10 tablets in a blister. 2 or 3 blisters per carton.

Prescription status

Prescription only.

Manufacturer

JSC “Farmak”

Location and address of manufacturer

63, Frunze str., Kyiv, 04080

Date of the last revision

25.06.2015