SUMMARY PRODUCT CHARACTERISTIC (SPC)

ENALAPRIL-H

1. Name of the medicinal product – Enalapril-H

2. Qualitative and Quantitative Composition

Each tablet contains:

active ingredients: enalapril maleate – 10 mg, hydrochlorothiazide – 25 mg.

For a full list of excipients, see section 6.1

3. Pharmaceutical form

White biconvex scored odorless tablets.

4. Clinical particulars

4.1 Therapeutic indications

Enalapril-H (enalapril and hydrochlorothiazide) is indicated for:

• Treatment of essential hypertension in patients for whom this combination therapy is appropriate.

In using Enalapril-H consideration should be given to the risk of angioedema (see Special warnings and precautions for use).

Enalapril-H is not indicated for initial therapy. Patients in whom enalapril and diuretic are initiated simultaneously can develop symptomatic hypotension (see Interaction with other medicinal products and other forms of interaction).

Patients should be titrated on individual drugs. If the fixed combination represents the dose and dosing frequency determined by this titration, the use of Enalapril-H may be more convenient in the management of patients. If during maintenance therapy dosage adjustment is necessary, it is advisable to use the individual drugs.

Geriatrics (> 65 years of age): See Dosage and administration.

Pediatrics (< 18 years of age): Enalapril-H is not recommended in this age group.

4.2 Posology and method of administration

The drug is intended for oral treatment.

The dosage of the drug is based primarily on the experience with its active substance Enalapril maleate. The usual dose is one tablet once daily. If required, the dose may be increase to two tablets once daily.

For most patients, 20 mg (exceptionally 40 mg) enalapril maleate or 50 mg hydrochlorothiazide a day is sufficient; therefore, not more than two Enalapril-H 10 mg/25 mg tablets a day are recommended. If no satisfactory response is achieved, addition of a second drug or changed therapy is recommended (see sections 4.3, 4.4, 4.5 and 5.1).

Prior diuretic therapy

Symptomatic hypotension may occur following the initial dose of the drug; this is more likely in patients who are volume and/or salt depleted as a result of prior diuretic therapy. The diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Enalapril-H 10 mg/25 mg.

Dosage in renal insufficiency

Thiazide diuretics may not be appropriate for patients with renal impairment. They are ineffective in patients with creatinine clearance values of 0.5 ml/s or less (i.e. moderate and severe renal insufficiency).

In patients with creatinine clearance between 0.5 ml/s and 1.3 ml/s, treatment should be started with a suitable dose of individual active substances.

Dosage in elderly patients

In clinical studies, the efficacy and tolerability of enalapril maleate and hydrochlorothiazide, administered concomitantly, were similar in both elderly and younger hypertensive patients.

Dosage in children

Safety and efficacy in children have not been established.

There is no time limit to the duration of treatment.

4.3 Contraindications

Enalapril-H is contraindicated in:

- Patients who are hypersensitive to this product or to any ingredient in the formulation. For a complete listing, see List of excipients.
- Patients with a history of angioneurotic edema relating to previous treatment with an angiotensin converting enzyme inhibitor.
- Renal artery stenosis.
- Severe hepatic impairment.
- Primary hyperaldosteronism (Conn's syndrome).
- Addison's disease.
- Porphyria.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- 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.
- Concomitant use of angiotensin converting enzyme inhibitors (ACEIs) – including the enalapril component of Enalapril-H with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR < 60 ml/min/1.73 m2) is contraindicated (see Special warnings and precautions for use, Cardiovascular, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal, and Interaction with other medicinal products and other forms of interaction, Dual Blockade of the Renin-Angiotensin System (RAS) with ACEIs, ARBs or aliskiren-containing drugs).
- Enalapril-H is contraindicated in combination with a neprilysin inhibitor (e.g., sacubitril). Do not administer Enalapril-H within 36 hours of switching to or from sacubitril/valsartan, a product containing a neprilysin inhibitor. (See Special warnings and precautions for use and Special warnings and precautions for use.)

4.4 Special warnings and precautions for use

Serious Warnings and Precautions

• When used in pregnancy, angiotensin converting enzyme (ACE) inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected, Enalapril-H should be discontinued as soon as possible.

Hypotension and electrolyte/fluid imbalance

As with other antihypertensive agents, symptomatic hypotension may occur in some patients. This is rarely seen in uncomplicated hypertensive patients but is more likely in the presence of fluid or electrolyte imbalance (e.g. volume depletion, hyponatraemia, hypochloraemic alkalosis, hypomagnesaemia or hypokalaemia) which may occur from prior diuretic therapy, dietary salt

restriction, dialysis, or during intercurrent diarrhoea or vomiting (see sections 4.5 and 4.8). Determination of serum electrolytes should be performed at appropriate intervals in such patients.
Particular consideration should be given when therapy is administered to patients with ischaemic heart or cerebrovascular disease because an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. In hypertensive 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, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of Enalapril-H 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, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses. Following restoration of effective blood volume and pressure, reinstitution of therapy at reduced dosage may be possible; or either of the components may be used appropriately alone. In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Enalapril-H. 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 Enalapril-H may be necessary.

Renal function impairment

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. Fixed combinations of enalapril and hydrochlorothiazide should not be prescribed to patients with renal insufficiency (creatinine clearance < 1.3 ml/s or 80 ml/min and > 0.5 ml/s or 30 ml/min) until titration of the individual active substances has shown the need for the doses present in the combination tablet. Some hypertensive patients with no apparent pre-existing renal disease who take enalapril concomitantly with a diuretic may develop minor and transient increases in serum urea and creatinine levels (see Special warnings and precautions for use, Enalapril maleate, Renal function impairment; Hydrochlorothiazide, Renal function impairment in section 4.4). If this occurs during therapy with a fixed combination of enalapril and hydrochlorothiazide, therapy should be discontinued. Reinstitution of therapy at reduced dosage may be possible, or either of the components may be used appropriately alone. This situation should raise the possibility of underlying renal artery stenosis (see Special warnings and precautions for use, Enalapril maleate, Renovascular hypertension in section 4.4).

Hyperkalaemia

The combination of enalapril and a low-dose diuretic cannot exclude the possibility of hyperkalaemia (see Special warnings and precautions for use, Enalapril maleate, Hyperkalaemia in section 4.4).

Lithium

The combination of lithium with enalapril and diuretic agents is generally not recommended (see section 4.5).

Paediatric population

Safety and efficacy in children has not been established.

Enalapril maleate

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared with monotherapy. Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended for every patient, particularly a patient with diabetic nephropathy (see sections 4.5 and 5.1).
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy. This refers to the prescription candesartan or valsartan as adjunctive therapy to an ACE inhibitor in patients with chronic heart failure. Implementation of dual RAAS blockade under observation expert and mandatory monitoring of renal function, water-electrolyte proportions and arterial pressure is possible in patients with chronic heart failure with hypersensitivity to aldosterone antagonists (spironolactone), which can be observed persistence of symptoms of chronic heart failure, irrespective of on the implementation of the second of adequacy of therapy.

Aortic stenosis/hypertrophic cardiomyopathy

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

Renal function impairment

Renal failure has been reported in association with enalapril and has been mainly seen in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognized promptly and treated appropriately, renal failure when associated with therapy with enalapril is usually reversible (see section 4.2 and Special warnings and precautions for use, Enalapril maleate and hydrochlorothiazide, Renal function impairment; Hydrochlorothiazide, renal function impairment in section 4.4).

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 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 enalapril is therefore not recommended.

Haemodialysis patients

The use of enalapril is not indicated in patients requiring dialysis for renal failure. Hypersensitivity, anaphylactoid reactions (facial swelling, flushing, hypotension and dyspnoea) have been reported in patients dialysed with high-flux membranes (e.g., AN 69) and treated concomitantly with an ACE inhibitor. This combination should therefore be avoided. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hepatic failure

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 (see Special warnings and precautions for use, Hydrochlorothiazide, Hepatic disease in section 4.4).

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.

Hyperkalaemia

ACE inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. The risk factors for the development of hyperkalaemia include 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 the use of other drugs associated with increases in serum potassium (e.g., heparin, trimethoprim or co-trimoxazole, also known as trimethoprim/sulfamethoxazole, and especially aldosterone antagonists or angiotensin receptor blockers). 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. Hyperkalaemia can cause serious, sometimes fatal, arrhythmias. Potassium-sparing diuretics and angiotensin receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see Hydrochlorothiazide section 4.5).

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 Special warnings and precautions for use, Hydrochlorothiazide, Metabolic and endocrine effects in section 4.4 and section 4.5).

Hypersensitivity/angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx occur rarely during treatment with angiotensin-converting enzyme inhibitors, including enalapril maleate. This may occur at any time during treatment. If angioedema occurs, treatment should be discontinued immediately and the patient monitored until all the symptoms resolve. The patient cannot be discharged before complete resolution of symptoms.

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. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. 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 taking ACE inhibitors have a higher incidence of angioedema compared to patients of other racial origin.

Patients with a history of angioedema unrelated to ACE-inhibitor therapy are at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3). Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with

sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of enalapril. Treatment with enalapril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5). Concomitant use of ACE inhibitors with racecadotril, mammalian target of rapamycin (mTOR) inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

Anaphylactoid reactions during desensitisation

Patients receiving ACE inhibitors can rarely experience life-threatening, allergy-like (anaphylactoid) reactions during desensitisation with bee or wasp venom. These reactions can be avoided by temporarily withholding ACE-inhibitor therapy prior to each desensitisation.

Anaphylactoid reactions during LDL apheresis

Patients receiving ACE inhibitors may experience life-threatening, allergy-like (anaphylactoid) reactions during low-density lipoprotein (LDL) apheresis with dextran sulphate. These reactions can be avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

Cough

Persistent, dry, non-productive cough can occur during treatment with ACE inhibitors, but it resolves after discontinuation of therapy. It 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 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 (see section 4.5).

Pregnancy

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Ethnic differences

As with other angiotensin-converting enzyme inhibitors, enalapril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Hydrochlorothiazide

Renal function impairment

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min or below (i.e., moderate or severe renal insufficiency) (see section 4.2 and Special warnings and precautions for use, Enalapril maleate and hydrochlorothiazide, Renal function impairment; Enalapril maleate, Renal function impairment in section 4.4).

Enalapril-H should not be administered to patients with renal insufficiency (creatinine clearance ≤80 ml/min) until titration of the individual components has shown the need for the doses present in the combination tablet.

Hepatic disease

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of electrolyte balance may precipitate hepatic coma (see Special warnings and precautions for use, Enalapril maleate, Hepatic failure in section 4.4).

Metabolic and endocrine effects

Thiazide diuretic therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see Special warnings and precautions for use, Enalapril maleate, Diabetic patients in section 4.4).

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy; however, at the 12.5 mg dose of hydrochlorothiazide, minimal or no effect was reported. In addition, in clinical studies with 6 mg of hydrochlorothiazide no clinically significant effect on glucose, cholesterol, triglycerides, sodium, magnesium or potassium was reported.

Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. This effect on hyperuricaemia appears to be dose-related, and is not clinically significant at the 6 mg dose of hydrochlorothiazide. In addition, enalapril may increase urinary uric acid and thus attenuate the hyperuricaemic effect of hydrochlorothiazide.

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides (including hydrochlorothiazide) can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloremic alkalosis). Warning signs of fluid or electrolyte imbalance are xerostomia, thirst, weakness, lethargy, somnolence, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Although hypokalaemia may develop during use of thiazide diuretics, concurrent therapy with enalapril may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients with inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5).

Hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and does usually not require treatment.

Thiazide diuretics may decrease urinary calcium excretion and cause intermittent and slight elevation of serum calcium. A marked increase in serum calcium may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Anti-doping test

Hydrochlorothiazide contained in this medicinal product can produce a positive analytic result in an anti-doping test.

Hypersensitivity

In patients receiving thiazide diuretics, hypersensitivity reactions may occur with or without a history of allergy or asthma. Exacerbation or activation of systemic lupus erythematosus has also been reported.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures, such as limited exposure to sunlight and UV rays, and, in case of exposure, adequate

protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Sulfonamide or sulfonamide derivative drugs can cause a hypersensitivity reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue the drug as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulphonamide or penicillin allergy.

Patients with lactose intolerance

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Serious Drug Interactions

• Concomitant use of lithium and Enalapril-H is not recommended.

Other antihypertensive agents

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

Lithium

Concomitant use of diuretics, ACE inhibitors and lithium may cause reversible increases in serum lithium concentrations and lithium toxicity. Concomitant use of thiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors.

Concomitant use is not recommended but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4.). Refer to the prescribing information for lithium preparations before use of such preparations.

Nonsteroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 (COX-2) Inhibitors

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

The coadministration of NSAIDs (including COX-2 inhibitors) and angiotensin II receptor antagonists or ACE inhibitors exert an additive effect on the increase in serum potassium, whereas renal function may decrease, 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.

Enalapril maleate

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated

with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended for every patient, particularly a patient with diabetic nephropathy (see sections 4.5 and 5.1). The concomitant use of Enalapril-H with aliskiren-containing products is contraindicated in patients with diabetes mellitus or moderate/severe renal impairment (GFR < 60 ml/min/1.73 m2) (see sections 4.5 and 5.1).
In some cases, when the simultaneous use of ACE inhibitors and angiotensin II receptor blockers is absolutely indicated, therapy should be initiated under close medical supervision with monitoring of renal function, water-electrolyte proportions and arterial pressure.

Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with enalapril. The use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes, particularly in patients with impaired renal function, may cause significant increases in serum potassium. Care should also be taken when enalapril is co-administered with other agents that increase serum potassium, such as trimethoprim and co-trimoxazole (trimethoprim/sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of enalapril with the above-mentioned drugs is not recommended. If concomitant use of any of these agents is deemed appropriate due to hypokalaemia, they should be used with great caution and with frequent monitoring of serum potassium (see section 4.4).

Ciclosporin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

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 sections 4.2 and 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic or by increasing volume or salt intake.

Tricyclic antidepressants/antipsychotics/anaesthetics

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sacubitril/valsartan

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see sections 4.3 and 4.4).

Racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors (see section 4.5); patients should be carefully monitored to confirm that the desired effect is being obtained.

Antidiabetics (oral hypoglycaemic agents and insulin)

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetics (insulins, oral hypoglycemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycaemia. This phenomenon is more likely to occur during the first weeks of

combined treatment and in patients with renal impairment (see sections 4.4 and 4.8). Long-term controlled clinical trials with enalapril have not confirmed these findings and do not preclude the use of enalapril in diabetic patients. It is advised, however, that these patients be monitored. The use of antidiabetic drugs and thiazide diuretics may require dosage adjustment of the antidiabetic drug.

Alcohol

Alcohol enhances the antihypertensive effect of ACE inhibitors.

Antacids

Antacids may decrease the bioavailability of ACE inhibitors.

Acetylsalicylic acid, thrombolytics and beta-blockers

Enalapril can be safely administered concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics and beta-blockers.

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 enalapril.

Cimetidine

Enalapril half-life may be reduced at simultaneous use of Enalapril-H and cimetidine.

Hydrochlorothiazide

Nondepolarizing muscle relaxants

Thiazides may increase the responsiveness to tubocurarine.

Alcohol, barbiturates, or opioid analgesics

Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)

Dosage adjustment of the antidiabetic drug may be required (see section 4.4 and 4.8).

Cholestyramine and colestipol resins

Anionic exchange resins may reduce the absorption of hydrochlorothiazide. 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.

Increasing the QT Interval (e.g., quinidine, procainamide, amiodarone, sotalol)

Increased risk of torsades de pointes.

Digitalis glycosides

Hypokalaemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Corticosteroids, ACTH

Concomitant use with thiazide diuretics results in intensified electrolyte depletion, particularly hypokalaemia.

Kaliuretic diuretics (e.g., furosemide), carbenoxolone, or laxative abuse

Hydrochlorothiazide may increase the loss of potassium and/or magnesium.

Pressor amines (e.g. adrenaline)

Thiazides may decrease the response to pressor amines (see section 4.5).

Cytostatics (e.g., cyclophosphamide, methotrexate)

Thiazides may reduce the renal excretion of cytotoxic drugs and potentiate their myelosuppressive effects.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started. ACE inhibitor therapy exposure 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) (see section 5.3). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

There is limited experience with hydrochlorothiazide during pregnancy, especially duringthe first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. As it can reduce plasma volume as well as uteroplacental blood flow, its use during the second and third trimesters may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, hypoglycaemia, disturbance of electrolyte balance and thrombocytopenia. Prolonged exposure to hydrochlorothiazide during the third trimester of pregnancy may cause a foeto-placental ischemia and growth retardation.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breast-feeding

Enalapril

Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of Enalapril-H 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 Enalapril-H in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

Hydrochlorothiazide

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Enalapril-H during breast feeding is not recommended. If Enalapril-H is used during breast feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines, it should be taken into account that occasionally dizziness and weariness may occur (see section 4.8).

4.8 Undesirable effects

Enalapril/hydrochlorothiazide is usually well-tolerated. In clinical studies, side effects have usually been mild and transient, and in most instances have not required interruption of therapy.

The most common side effects reported during clinical study with enalapril/hydrochlorothiazide were headache and cough.

The following undesirable side effects have been reported with enalapril/hydrochlorothiazide, enalapril alone or hydrochlorothiazide alone either during clinical studies or after the drug was marketed:
- very common (≥ 1/10),
- common (≥ 1/100 to < 1/10),
- uncommon (≥ 1/1000 to < 1/100),
- rare (≥ 1/10,000 to < 1/1000),
- very rare (< 1/10,000),
- not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequency of undesirable effects listed by individual organ systems:
Neoplasms benign, malignant and unspecified (incl cysts and polyps)
- not known: non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma) ±
Blood and lymphatic system disorders
- uncommon: anaemia (including aplastic and haemolytic)
- rare: neutropenia, decreases in haemoglobin and haematocrit, thrombocytopenia, agranulocytosis, leukopenia, bone marrow depression, pancytopenia, lymphadenopathy,
autoimmune diseases
Endocrine disorders
- not known: syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders
- common: hypokalaemia, increase of cholesterol, increase of triglycerides, hyperuricaemia
- uncommon: hypoglycaemia (see section 4.4), hypomagnesaemia, gout*
- rare: increased blood glucose
- very rare: hypercalcaemia (see section 4.4).
Nervous system and psychiatric disorders
- common: headache, depression, syncope, taste alteration
- uncommon: confusion, insomnia, drowsiness, nervousness, paraesthesia, vertigo, decreased libido*
- rare: dream abnormality, sleep disorders, paresis (due to hypokalaemia)
Eye disorders
- very common: blurred vision
- not known: choroidal effusion
Ear and labyrinth disorders
- uncommon: tinnitus
Cardiac and vascular disorders
- very common: dizziness
- common: hypotension, orthostatic hypotension, rhythm disorders, tachycardia, chest pain
- uncommon: flushing, palpitations, myocardial infarction or cerebrovascular accident†, possibly secondary to excessive hypotension in high risk patients (see section 4.4)
- rare: Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders
- very common: cough
- common: dyspnoea
- uncommon: rhinorrhoea, sore throat and hoarseness, bronchospasm/asthma
- rare: pulmonary infiltrates, respiratory distress (including pneumonitis and pulmonary oedema), rhinitis, allergic alveolitis/eosinophilic pneumonia

Gastrointestinal disorders

- very common: nausea
- common: diarrhoea, abdominal pain
- uncommon: ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritations, dry mouth, peptic ulcer, flatulence*
- rare: stomatitis/aphthous ulcerations, glossitis
- very rare: intestinal angioedema

Hepatobiliary disorders

- rare: hepatic failure, hepatic necrosis (may be fatal), hepatitis – either hepatocellular or cholestatic, jaundice, cholecystitis (in particular in patients with pre-existing cholelithiasis)

Skin and subcutaneous tissue disorders

- common: rash (exanthema), hypersensitivity/angioedema: angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (see section 4.4)
- uncommon: pruritus, diaphoresis, alopecia, urticaria
- rare: erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, purpura, cutaneous lupus erythematosus, erythroderma, pemphigus

A symptom complex has been reported: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

Musculoskeletal and connective tissue disorders

- common: muscle cramps**
- uncommon: arthralgia*

Renal and urinary disorders

- uncommon: renal dysfunction, renal failure, proteinuria
- rare: oliguria, interstitial nephritis

Reproductive system and breast disorders

- uncommon: impotence
- rare: gynaecomastia

General disorders and administration site conditions

- very common: asthenia
- common: chest pain, fatigue
- uncommon: malaise, fever

Investigations

- common: hyperkalaemia, increases in serum creatinine
- uncommon: increases in serum urea, hyponatraemia
- rare: elevations of liver enzymes, elevations of serum bilirubin

* Only seen with doses of hydrochlorothiazide 12.5 mg and 25 mg.

** The frequency of muscle cramps as common pertains to doses of hydrochlorothiazide 12.5 mg and 25 mg, whereas, the frequency of the event is uncommon as it pertains to 6 mg doses of hydrochlorothiazide.

± Non-melanoma skin cancer:

Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Incidence rates were comparable to those in the placebo and active control groups in the clinical trials.

If severe undesirable effects occur, treatment should be discontinued.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via "Arpimed" LLC by going to www.arpimed.com and fill out the appropriate form ″Report an adverse reaction or inefficiency of drug″. Hotline number: (+374 55) 05 79 86. And by using "Centre of Drug and Medical Technology Expertise" SNPO, going to the site: www.pharm.am in ″Report about adverse effect of medicine″ section and fill out the ″Report of adverse reaction or manufacturing problem of medicinal product″. Hotline numbers: +37410200505; +37496220505.

4.9. Overdose
No specific information is available on the treatment of overdose with the fixed combination of enalapril and hydrochlorothiazide. Therapy with the fixed combination of enalapril and hydrochlorothiazide should be discontinued and the patient observed closely. The first measures include induction of emesis and/or gastric lavage to immediately remove the ingested drug. Treatment is symptomatic and supportive – established procedures should be used to correct dehydration, electrolyte imbalance and hypotension.

Enalapril maleate
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 100- and 200-fold higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of enalapril maleate, 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, the active metabolite of enalapril, may be removed by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

Hydrochlorothiazide
The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias.

5. Pharmacological properties
5.1 Pharmacodynamic properties
Combined antihypertensive drugs; C09BA02.
Enalapril maleate
Enalapril is an ACE inhibitor. In the body, it is rapidly metabolised to enalaprilat, which is a potent ACE inhibitor.
The main effects of the inhibition of ACE are: reduced concentrations of angiotensin II and aldosterone in the blood circulation, inhibition of the activity of tissue angiotensin II, increased renin release, stimulation of vasodepressor kallikrein-kinin system, suppression of the sympathetic nervous

system, and increased release of prostaglandins and the relaxing factor from vascular endothelium. Enalapril thus blocks the degradation of bradykinin, a potential vasodepressor peptide. However, the role of bradykinin in the therapeutic effects of enalapril remains to be elucidated. While the mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the rennin-angiotensin-aldosterone system, which plays a major role in the regulation of blood pressure, enalapril is antihypertensive even in patients with low-renin hypertension.

The peak effect of enalapril occurs after 6 to 8 hours. The effect usually persists for up to 24 hours, thus allowing once- to twice-daily dosing.

Enalapril maleate - hydrochlorothiazide

Hydrochlorothiazide is a diuretic and antihypertensive agent which increases plasma renin activity.

Although enalapril alone is antihypertensive even in patients with low-renin hypertension, concomitant administration of hydrochlorothiazide in these patients leads to greater reduction of blood pressure.

Concomitant administration of an ACE inhibitor and hydrochlorothiazide is therefore reasonable when each drug alone is not sufficiently effective. This co-administration makes possible a better therapeutic effect at lower doses of enalapril and hydrochlorothiazide and fewer undesirable effects.

The antihypertensive effect of the combination usually lasts for up to 24 hours; therefore, once- to twice-daily dosing is sufficient.

Dual Blockade

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Non-melanoma skin cancer

Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively.

High HCTZ use (≥ 50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23–1.35) for BCC and 3.98 (95% CI: 3.68–4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls,

using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7–2.6) increasing to OR 3.9 (3.0–4.9) for high use (~25,000 mg) and OR 7.7 (5.7–10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

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 maleate is approximately 60%. Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin-converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur 3 to 4 hours after an oral dose of enalapril maleate. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril. Except for conversion to enalaprilat, there is no evidence of significant metabolism of enalapril. The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently associated with binding to ACE. In subjects with normal renal function, steady-state serum concentrations of enalaprilat were achieved by the fourth day of administration of enalapril maleate. The absorption of oral enalapril maleate is not influenced by the presence of food in the gastro-intestinal tract. The extent of absorption and hydrolysis of enalapril are similar for the various doses in the recommended therapeutic range.

Distribution

Studies in dogs indicate that enalapril crosses the blood-brain barrier poorly, if at all; enalaprilat does not enter the brain. Enalapril crosses the placental barrier. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

Metabolism

Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril. Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney.

Elimination

Excretion of enalapril is primarily renal. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and unchanged enalapril. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril maleate is 11 hours. When plasma levels of hydrochlorothiazide have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours.

Lactation

After a single 20 mg oral dose in five postpartum women, the average peak enalapril milk level was 1.7 μg/L (range 0.54 to 5.9 μg/L) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1.7 μg/L (range 1.2 to 2.3 μg/L); peaks occurred at various times over the 24-hour period. Using the peak milk level data, the estimated maximum intake of an exclusively breast-fed infant would be about 0.16% of the maternal weight-adjusted dosage. A woman who had been taking oral enalapril 10 mg daily for 11 months had peak enalapril milk levels of 2 μg/L 4 hours after a dose and peak enalaprilat levels of 0.75 μg/L about 9 hours after the dose. The total amount of enalapril and enalaprilat measured in milk during the 24 hour period was 1.44 μg/L and 0.63 μg/L of milk respectively.

Enalaprilat milk levels were undetectable (< 0.2 μg/L) 4 hours after a single dose of enalapril 5 mg in one mother and 10 mg in two mothers; enalapril levels were not determined.

Concomitant administration of enalapril and hydrochlorothiazide has no effect on the bioavailability and pharmacokinetics of separate drugs.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Toxicological studies in mice and rats indicated lower acute toxicity of enalapril and hydrochlorothiazide combination compared to enalapril maleate. The oral LD50 values of the combination exceed 5 g/kg in both mice and rats. Prolonged administration of the mentioned combination caused changes in kidney function and morphological damage to the gastrointestinal tract.

Reproduction toxicity studies in laboratory animals demonstrated foetotoxic effects of Enalapril maleate and hydrochlorothiazide, administered either separately or in combination.

No mutagenicity of enalapril and hydrochlorothiazide combination was established. Since enalapril and hydrochlorothiazide alone are not carcinogenic, the same may be expected of the combination.

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose,
Lactose monohydrate,
Povidone,
Maize starch,
Sodium starch glycolate,
Magnesium stearate,
Calcium hydrogen phosphate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Do not use this medicine after the expiry date.

6.4 Special precautions for storage

Store out of reach of children, in a dry place, protected from light at a temperature below 25^0C.

6.5 Nature and contents of container

2 blister packets with 10 tablets in each with leaflet in the cardboard box.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

"ARPIMED" LLC
Kotayki Marz, Abovyan, 2204, 2nd Micro-District, 19 Building, Republic of Armenia
Tel.: (374) 222 21703
Fax: (374) 222 21924

8. Date of first authorisation

12.11.2004

9. Date of revision of the text