Summary of Product Characteristics

1. Name of the medicinal product

KADRIL PLUS 10 mg+25mg tablets
KADRIL PLUS 20 mg+12,5mg tablets

2. Qualitative and quantitative composition

KADRIL PLUS 10 mg+25mg tablets
Each tablet contains 10 mg of enalapril maleate and 25 mg of hydrochlorothiazide.
KADRIL PLUS 20 mg+ 12,5 mg tablets
Each tablet contains 20 mg of enalapril maleate and 12.5 mg of hydrochlorothiazide.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet

4. Clinical particulars

4.1 Therapeutic indications

Treatment of essential hypertension.
This fixed dose combination is indicated in patients whose blood pressure is not adequately controlled with enalapril alone.
This fixed dose may also replace the combination of 20 mg enalapril maleate and 12.5 mg hydrochlorothiazide in patients who have been stabilised on the individual active substances given in the same proportions as separate medications.
(See sections 4.3, 4.4, 4.5 and 5.1).
This fixed dose combination is not suitable for initial therapy.

4.2 Posology and method of administration

Posology
The recommended dosage is one tablet, taken once daily.
Individual dose titration with both active substances may be recommended.
When clinically appropriate, direct change from ACE inhibitor monotherapy to the fixed combination may be considered.
Renal impairment
In patients with creatinine clearance of >30 and <80 ml/min, enalapril/hydrochlorothiazide 20 mg/12.5 mg should be used only after titration of the individual components. Loop diuretics are preferred to thiazides in this population. The dose of KADRIL PLUS should be kept as low as possible (see section 4.4).
Potassium and creatinine should be monitored periodically in these patients, e.g. every 2 months when the treatment has been stabilised (see section 4.4).
In patients with creatinine clearance of < 30 ml/min, see section 4.3.
Special populations
In patients with sodium/volume depletion, the initial dose is 5 mg of enalapril or lower. An individual and progressive introduction of enalapril and hydrochlorothiazide is recommended.
Elderly
In clinical studies the efficacy and tolerability of KADRIL PLUS, administered concomitantly, were similar in both elderly and younger hypertensive patients.
In case of physiological renal impairment, titration with enalapril alone is recommended prior to using the fixed combination.
Paediatric population
The safety and efficacy of KADRIL PLUS 20 mg +12.5 mg Tablets in children and adolescents aged under 18, has not been established.
Method of administration
For oral administration with or without food.

4.3 Contraindications

• Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
• Severe renal impairment (creatinine clearance ≤30 ml/min).
• Anuria.
• History of angioneurotic oedema associated with previous ACE-inhibitor therapy.
• Hereditary or idiopathic angioedema.
• Hypersensitivity to sulfonamide-derived drugs.
• Second and third trimesters of pregnancy (see section 4.4 and 4.6).
• Severe hepatic impairment.
• The concomitant use of KADRIL PLUS 20 mg/12.5 mg Tablets with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Enalapril-Hydrochlorothiazide
Hypotension and Electrolyte Fluid Imbalance
Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving enalapril/hydrochlorothiazide, symptomatic hypotension is more likely to occur if the patient has been volume-depleted, e.g., by diuretic therapy, dietary salt restriction, diarrhoea or vomiting (see sections 4.5 and 4.8). Regular determination of serum electrolytes should be performed at appropriate intervals in such patients. Special attention should be paid to patients with ischemic heart or cerebrovascular disease in whom 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/hydrochlorothiazide and/or diuretic is adjusted.
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 with normal or low blood pressure, additional lowering of systemic blood pressure may occur with enalapril/hydrochlorothiazide. This effect is expected and is usually not a reason to stop treatment. If hypotension becomes symptomatic, a dose reduction and/or discontinuation of the diuretic and/or enalapril may be necessary.
Renal Impairment
Enalapril/hydrochlorothiazide should not be administered to patients with renal insufficiency (creatinine clearance <80 ml/min and >30 ml/min) until titration of enalapril has shown the need for the dose present in this formulation (see section 4.2).
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 (see section 4.4). If this occurs, therapy with enalapril/hydrochlorothiazide should be discontinued. This situation should raise the possibility of underlying renal artery stenosis (see section 4.4).
The use of enalapril/hydrochlorothiazide in combination with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60ml/min/1.73 m2) (see section 4.3).
Hyperkalaemia
The combination of enalapril and a low-dose diuretic cannot exclude the possibility of an hyperkalaemia to occur (see section 4.4).
Lithium
The combination of lithium with enalapril and diuretic agents is generally not recommended (see section 4.5).
Paediatric population
The safety and efficacy of this product have not been demonstrated in controlled studies in children.

Excipients
KADRIL PLUS 20 mg/12.5 mg Tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Enalapril

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

Renal 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 (see section 4.2 and section 4.4). Routine monitoring of potassium and creatinine should be part of normal medical practice for these patients.

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. 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.

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). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (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.

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 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
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including enalapril. Risk factors for the development of hyperkalaemia 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, co-trimoxazole also known as trimethoprim/sulphametoxazole). 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. 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 4.4 and section 4.5).

Diabetic Patients

Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor should be told to closely monitor for hypoglycemia, especially during the first month of combined use (see section 4.4 and section 4.5).

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 maleate. This may occur at any time during treatment. In such cases, enalapril/hydrochlorothiazide 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. 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 receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to white patients. However, in general it appears that black patients have an increased risk for angioedema.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)

Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5).

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 LDL-Apheresis

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

Cough

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

Surgery/Anaesthesia

Enalapril blocks angiotensin II formation and therefore impairs the ability of patients undergoing major surgery or anaesthesia with agents that produce hypotension to compensate via the renin-angiotensin system. Hypotension which occurs due to this mechanism 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 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 section 4.4).

Hypovolemia secondary to sodium and water loss induced by the diuretic at the start of treatment, results in a reduction in glomerular filtration. This can result in an increase in blood urea and creatinine.

This transient renal functional impairment is of no consequence in patients with normal renal function but may aggravate pre-existing renal failure.

Hepatic Impairment

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma (see section 4.4).

Metabolic and Endocrine Effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents including insulin, may be required (see section 4.4). Thiazides may decrease serum sodium, magnesium and potassium levels.

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 contained in enalapril/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 hypochloraemic 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).

In patients with a congenital or drug-induced long QT interval, hypokalaemia promotes the occurrence of severe arrhythmias, particularly a potentially fatal torsades de pointes, especially in the presence of bradycardia.

Potassium levels should be monitored regularly, beginning the first week of treatment.

Sodium levels should be checked before starting treatment and at regular intervals. Any diuretic treatment may cause hyponatraemia, sometimes with serious consequences. The decrease in serum sodium can be initially asymptomatic, regular monitoring is essential and may be more common in populations at risk such as elderly, malnourished subjects and cirrhotic patients (see sections 4.8 and 4.9).

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

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of latent hyperparathyroidism. Thiazides should be discontinued before testing parathyroid function.

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

Anti-doping test

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

Hypersensitivity

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

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).

KADRIL PLUS tablets contain lactose. 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

Enalapril-Hydrochlorothiazide

Other Antihypertensive Agents

Concomitant use of these agents (e.g. beta-blockers, methyldopa, calcium channel blockers) 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

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/hydrochlorothiazide with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4.).

Non-Steroidal Anti-Inflammatory Drugs including selective cyclooxygenase-2 (COX-2) inhibitors

Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor or may decrease the diuretic, natriuretic and antihypertensive effects of diuretics.

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).

Dual Blockade of the Renin-angiotensin-aldosterone System

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 (e.g., by adding an ACE inhibitor to an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function.

Enalapril

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 4.4).

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).

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics

Epidemiological studies have suggested that 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 section 4.8).

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.

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.

mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)

Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see section 4.4)

Co-trimoxazole (trimethoprim/sulfamethoxazole)

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.4).

Hydrochlorothiazide

Non-depolarising Muscle Relaxants

Thiazides may increase the responsiveness to tubocurarine.

Alcohol, Barbiturates, Opioid Analgesics, Antidepressants

Potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs (Oral Agents and Insulin)

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

Treatment with a thiazide may influence glucose tolerance. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Cholestyramine and Colestipol Resins

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

Digitalis Glycosides

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

Amphotericin B (parenteral), corticosteroids, ACTH

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., Noradrenaline)
The effect of pressor amines may be decreased.
Cytostatics (e.g., Cyclophosphamide, Methotrexate)
Thiazides may reduce the renal excretion of cytotoxic drugs and potentiate their myelosuppressive effects.
Drugs used to treat gout (probenecid, sulfinpyrazone and allopurinol)
A dose adjustment of uricosuric agents may be necessary, as hydrochlorothiazide may increase the level of serum uric acid. An increase in the dose of probenecid or sulfinpyrazone may be necessary. Co-administration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.
Anticholinergic agents (eg. Atropine, biperiden)
Increase the bioavailability of thiazide diuretics by decreasing gastrointestinal motility and stomach emptying rate.
Salicylates
Hydrochlorothiazide may enhance the toxic effect of high dose salicylates on the central nervous system.
Methyldopa
Isolated cases of hemolytic anaemia occurring during concomitant use of hydrochlorothiazide and methyldopa have been reported.
Cyclosporin
Concomitant treatment with cyclosporin may increase the risk of hyperuricaemia and gout-type complications.
Drugs affected by serum potassium disturbances and increasing the QT interval
Periodic monitoring of serum potassium and ECG is recommended when enalapril/hydrochlorothiazide is administered in conjunction with drugs affected by serum potassium disturbances (eg. Digitalis glycosides and antiarrhythmics) and with the following medications increasing the risk of torsades de pointes (ventricular tachycardia), including some antiarrhythmic, because hypokalaemia is a predisposing factor to torsades de pointes (ventricular tachycardia):
- Anti-arrhythmic drugs class Ia (eg. quinidine, hydroquinidine, disopyramide, procainamide);
- Anti-arrhythmic drugs class III (eg. amiodarone, sotalol, dofetilide, ibutilide);
- Some anti-psychotics (eg. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol);
- Other (eg. bepridil, cisapride, diphemanil, IV erythromycin, halofantrine, mizolastine, pentamidine, terfenadine, vincamine IV).
Salts of calcium and vitamin D
Thiazide diuretics may increase serum concentrations of calcium due to decreased excretion. If calcium supplements must be prescribed, it will be necessary to monitor serum calcium levels and adjust the dose of calcium.
Interactions with biological tests
Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see section 4.4).
Carbamazepine
Risk of symptomatic hyponatraemia. Clinical and laboratory monitoring is required.
Iodinated contrast media
In case of dehydration caused by diuretics, the risk of acute renal failure is increased, especially when using large doses of iodinated contrast media.
Patients should be rehydrated before use.
Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
ACE-inhibitors:
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4).
The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).
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.
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) (see section 5.3).
Maternal oligohydramnios, presumably representing decreased foetal renal function, has occurred and may result in limb contractures, craniofacial deformations and hypoplastic lung development.
Should exposure to ACE inhibitors 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).
Hydrochlorothiazide:
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
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/hydrochlorothiazide in breast-feeding 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/hydrochlorothiazide 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/hydrochlorothiazide during breast-feeding is not recommended. If enalapril/hydrochlorothiazide is used during breast-feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

Enalapril/hydrochlorothiazide has minor or moderate influence on the ability to drive and use machines. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur (See section 4.8).

4.8 Undesirable effects

Side effects reported with enalapril/hydrochlorothiazide, enalapril alone or hydrochlorothiazide alone either during clinical studies or after the drug was marketed include:
[Very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).]
Blood and Lymphatic System Disorders:
uncommon: anaemia (including aplastic and haemolytic)
rare: neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, leukopenia, 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), hypomagnaesemia, gout*
rare: increase in blood glucose
very rare: hypercalcaemia
(see section 4.4)
Psychiatric Disorders:
common: depression
uncommon: insomnia, nervousness, decreased libido*
rare: dream abnormality, sleep disorders
Nervous System :
very common: dizziness
common: headache, syncope, taste alteration
uncommon: confusion, somnolence, paraesthesia, vertigo
rare: paresis (due to hypokalaemia)
Eye Disorders:
very common: blurred vision
Ear and Labyrinth Disorders:
uncommon: tinnitus
Cardiac Disorders:
common: rhythm disturbances, angina pectoris, tachycardia,
uncommon: palpitations, myocardial infarction possibly secondary to excessive hypotension in high risk patients (see section 4.4)
Vascular Disorders
common: hypotension, orthostatic hypotension
uncommon: flushing, 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/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (see section 4.4).
uncommon: diaphoresis, pruritus, urticaria, alopecia
rare: erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, purpura, cutaneous lupus erythematosus, erythroderma, pemphigus
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 (antinuclear antibody), elevated ESR (erythrocyte sedimentation rate), 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: gynecomastia
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 blood urea, hyponatraemia
rare: elevations of liver enzymes, elevations of serum bilirubin
* These ADRs are only relevant for doses of hydrochlorothiazide 12.5 mg as found in KADRIL PLUS 20 mg/12.5 mg Tablets and 25 mg.
† The frequency of muscle cramps as common pertains to doses of hydrochlorothiazide 12.5 mg as found in KADRIL PLUS 20 mg/12.5 mg Tablets and 25 mg, whereas, the frequency of the event is uncommon as it pertains to 6 mg doses of hydrochlorothiazide.

Additional side effects related to hydrochlorothiazide
Infections and infestations: Sialadenitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps):
Not known: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)
- 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).
Metabolism and nutrition disorders: glycosuria
Nervous system disorders: lightheadedness.
Disorders of skin tissue and subcutaneous: anaphylaxis.
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.

4.9 Overdose

No specific information is available on the treatment of overdosage with enalapril/hydrochlorothiazide.
Treatment
Treatment is symptomatic and supportive. Therapy with enalapril/hydrochlorothiazide should be discontinued and the patient observed closely. Suggested measures include induction of emesis, administration of activated charcoal, and administration of a laxative if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.
Enalapril Maleate
Symptoms
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.
Treatment
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

hemodialysis. (See section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

Hydrochlorothiazide

Symptoms

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.

In addition to the expected diuresis, overdosage of thiazides may produce varying degrees of lethargy that can progress to coma within hours, with minimal depression of respiration and cardiovascular function, and with no evidence of changes in serum electrolytes or dehydration. The mechanism of CNS depression induced by thiazides is unknown.

Gastric irritation and an increase of urea in the blood have been reported and changes in serum electrolytes, particularly in patients with impaired renal function.

From the clinical point of view, nausea, vomiting, hypotension, cramps, dizziness, drowsiness, in confusion, polyuria or oliguria up to anuria (by hypovolaemia) may occur.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors and diuretics

ATC code: C09B A02

Mechanism of action

ASSOCIATED WITH ENALAPRIL

Enalapril maleate is the maleate salt of enalapril, a derivative of two amino acids, L-alanine and L-proline. Angiotensin converting enzyme (ACE) 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 may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of enalapril remains to be elucidated.

ASSOCIATED WITH HYDROCHLOROTHIAZIDE

Hydrochlorothiazide is a thiazide diuretic which acts as a blood pressure-lowering agent by inhibiting fluid-expelling, which increase the tubular re-absorption of sodium in the cortical diluting segment.

It increases the urinary excretion of sodium and chloride and, to a lesser degree, the excretion of potassium and magnesium, thus increasing diuresis and exerting an anti-hypertensive effect.

Characteristics of antihypertensive activity

ASSOCIATED WITH ENALAPRIL

While the mechanism through which enalparil lowers blood pressure is believed to be primarily suppression of the renin-angiotensin aldosterone system, enalapril is antihypertensive even in patients with low-renin hypertension.

Administration of enalapril 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 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 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 short-term clinical 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 are at least additive. Enalapril may reduce or prevent the development of thiazide-induced hypokalaemia.
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.
ASSOCIATED WITH HYDROCHLOROTHIAZIDE
The time to onset of diuretic activity is approximately 2 hours. Diuretic activity reaches a peak after 4 hours and is maintained for 6 to 12 hours.
Above a certain dose, thiazide diuretics reach a plateau in terms of therapeutic effect whereas adverse reactions continue to multiply. When treatment is ineffective, increasing the dose beyond recommended doses serves no useful purpose and often gives rise to adverse reactions.
ASSOCIATED WITH THE COMBINATION
In clinical studies, the concomitant administration of enalapril and hydrochlorothiazide reduced blood pressure more significantly than either substance alone.
The administration of enalapril inhibits the renin-angiotensin-aldosterone system and tends to reduce the hydrochlorothiazide-induced potassium loss.
Combination of an ACE inhibitor with a thiazide diuretic produces a synergistic effect and also lessens the risk of hypokalaemia provoked by the diuretic alone.
Clinical safety and efficacy
ASSOCIATED WITH HYDROCHLOROTHIAZIDE
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

Co-administration of enalapril and hydrochlorothiazide in various doses has little or no effect on the bioavailability of these two substances.

ASSOCIATED WITH ENALAPRIL

Absorption

Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within 1 hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril maleate is approximately 60%. The absorption of oral enalapril is not influenced by the presence of food in the gastrointestinal tract.

Distribution

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 effective half-life for accumulation of enalapril following oral administration of multiple doses is 11 hours. In patients with normal renal function the concentrations of enalaprilat at the steady state were reached after four days of treatment.

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

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 breastfed 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.

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 following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency and time to steady state is delayed. (See section 4.2, Dosage in renal Insufficiency).

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

ASSOCIATED WITH HYDROCHLOROTHIAZIDE

Absorption

Oral absorption of hydrochlorothiazide is relatively rapid.

The bioavailability of hydrochlorothiazide varies between 60 and 80%. The time to peak plasma concentration (Tmax) varies between 1.5 and 5 hours, with a mean of about 4 hours.

Distribution

Protein binding is approximately 40%.

The mean plasma half-life in fasted individuals has been reported to be 5 to 15 hours.

Elimination

Hydrochlorothiazide is eliminated rapidly by the kidney and excreted unchanged (> 95%) in the urine. At least 61% of the oral dose is eliminated unchanged within 24 hours.

In renal and cardiac impairment, as in the elderly, the renal clearance of hydrochlorothiazide is reduced, and the elimination half-life increased. Elderly subjects also show increased peak plasma concentrations.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
Reproductive toxicity studies suggest that enalapril has no effects on fertility and reproductive performance in rats, and is not teratogenic. In a study in which female rats were dosed prior to mating through gestation, an increased incidence of rat pup deaths occurred during lactation.
Angiotensin converting enzyme inhibitors, as a class, have been shown to be foetotoxic (causing injury and/or death to the foetus) when given in the second or third trimester.

6. Pharmaceutical particulars

6.1 List of excipients

• lactose monohydrate,

• sodium bicarbonate,

• povidone,

• pregelatinized corn starch,

• corn starch,

• maleic acid,

• magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original packaging.

6.5 Nature and contents of container

Box of 20 round, biconvex, yellow, of 10 mg enalapril maleate + 25 mg hydrochlorothiazide, in blister pack (2 blisters x 10 tablets).

Box of 20 round, biconvex, white, of 20 mg enalapril maleate + 12,5 mg hydrochlorothiazide,in blister pack (2 blisters x 10 tablets)

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

ZADA Pharmaceuticals Ltd.
Donji Bistarac without number
75300 Lukavac
Bosnia and Herzegovina

8. Marketing authorisation number(s)
KADRIL PLUS, 20 tablets x (10 + 25) mg in box: 04-07.3-2-4861/15
KADRIL PLUS, 20 tablets x (20 + 12,5) mg in box: 04-07.3-2-4862/15

9. Date of first authorisation/renewal of the authorization
KADRIL PLUS, 20 tablets x (10 + 25) mg in box: 09.09.2015.
KADRIL PLUS, 20 tablets x (20 + 12,5) mg in box: 09.09.2015.

10. Date of revision of the text
11/2018