SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT

Thiapril

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Thiapril: each tablet contains 5 mg ramipril and 12.5mg hydrochlorothiazide

Excipient with known effect: lactose monohydrate 47.50 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL form

Tablets.

White or off white flat, bevel-edged, circular tablets with “MBN” engraved at the centre on one side. On the reverse side engraved with a “breakline” at the centre and “Th” above the “breakline”. No irregularities on surface, no capping and not collared or chipped.

4. Clinical particulars

4.1 Therapeutic indications

- Treatment of hypertension.

This fixed dose combination is indicated in patients whose blood pressure is not adequately controlled with ramipril alone or hydrochlorothiazide alone.

4.2 Posology and method of administration

Posology

Adults

The dose should be individualised according to the patient profile (see section 4.4) and blood pressure control. The administration of the fixed combination of ramipril and hydrochlorothiazide is usually recommended after dosage titration with one of the individual components. Thiapril should be started at the lowest available dosage. If necessary, the dose can be progressively increased to achieve target blood pressure; the maximum permitted doses are 10 mg of ramipril and 25 mg of hydrochlorothiazide daily.

Special populations

Diuretic-treated patients

In patients concurrently treated with diuretics, as hypotension may occur following initiation of the treatment, caution is recommended. Consideration must be given to reducing the diuretic dose or discontinuing the diuretic before starting treatment with thiapril.

Should discontinuation not be possible, it is recommended that treatment be initiated with the smallest possible dosage of ramipril (1.25 mg daily) in a free combination. It is recommended that, subsequently, a changeover be made to an initial daily dose of not more than 2.5 mg ramipril /12.5 mg hydrochlorothiazide.

Patients with renal impairment

Thiapril is contraindicated in severe renal impairment due to the hydrochlorothiazide component (creatinine clearance < 30 ml/min) (see section 4.3). Patients with impairment of renal function may require reduced doses of /.../. Patients with creatinine clearance levels between 30 and 60 ml/min should only be treated with the lowest fixed dose combination of ramipril and hydrochlorothiazide after administration of ramipril alone. The maximum permitted doses are 5 mg of ramipril and 25 mg of hydrochlorothiazide daily.

Patients with hepatic impairment

In patients with mild to moderate hepatic impairment, treatment with thiapril must be initiated only under close medical supervision and the maximum daily doses are 2.5 mg of ramipril and 12.5 mg of hydrochlorothiazide. Thiapril is contraindicated in severe hepatic impairment (see section 4.3).

Older people

Initial doses should be lower and subsequent dose titration should be more gradual because of greater chance of undesirable effects especially in very old and frail patients.

Paediatric population

The safety and efficacy of ramipril in children has not yet been established. Currently available data for thiapril are described in sections 4.8, 5.1, 5.2 and 5.3 but no specific recommendation on posology can be made.

Method of administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to the active substances or to any other ACE (Angiotensin Converting Enzyme) inhibitor, other thiazide diuretics, sulfonamides or to any of the excipients listed in section 6.1
- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or AIIRAs)
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5)
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney
- 2nd and 3rd trimester of pregnancy (see sections 4.4 and 4.6)
- Lactation (see section 4.6)
- Severe impairment of renal function with a creatinine clearance below 30 ml/min in undialysed patients
- Clinically relevant electrolyte disturbances which may worsen following treatment with thiapril (see section 4.4)
- Severe impairment of liver function, hepatic encephalopathy
- The concomitant use of thiapril 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)

• Concomitant use with sacubitril/valsartan therapy. Ramipril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Special populations

Pregnancy: ACE inhibitors such as ramipril, or Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued ACE inhibitor/AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors/AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

• Patients at particular risk of hypotension

Patients with strongly activated renin-angiotensin-aldosterone system Patients with strongly activated renin-angiotensin-aldosterone system are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition, especially when an ACE inhibitor or a concomitant diuretic is given for the first time or at first dose increase. Significant activation of renin-angiotensin-aldosterone system is to be anticipated and medical supervision including blood pressure monitoring is necessary, for example in:
• Patients with severe hypertension
• Patients with decompensated congestive heart failure
• Patients with haemodynamically relevant left ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve)
• Patients with unilateral renal artery stenosis with a second functional kidney
• Patients in whom fluid or salt depletion exists or may develop (including patients with diuretics)
• Patients with liver cirrhosis and/or ascites
• Patients undergoing major surgery or during anaesthesia with agents that produce hypotension.
Generally, it is recommended to correct dehydration, hypovolaemia or salt depletion before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed out against the risk of volume overload).

Surgery
It is recommended that treatment with angiotensin converting enzyme inhibitors such as ramipril should be discontinued where possible one day before surgery.

Patients at risk of cardiac or cerebral ischemia in case of acute hypotension
The initial phase of treatment requires special medical supervision.

• Primary Hyperaldosteronism
The combination ramipril + hydrochlorothiazide does not represent a treatment of choice for primary hyperaldosteronism. If ramipril + hydrochlorothiazide is used in a patient with primary hyperaldosteronism, then careful monitoring of plasma potassium level is required.

• Older people See section 4.2.

• Patients with liver disease
Electrolyte disturbances due to diuretic therapy including hydrochlorothiazide may cause hepatic encephalopathy in patients with liver disease.

Monitoring of renal function
Renal function should be assessed before and during treatment and dosage adjusted especially in the initial weeks of treatment. Particularly careful monitoring is required in patients with renal impairment (see section 4 4.2). There is a risk of impairment of renal function, particularly in patients with

congestive heart failure or after renal transplant or with renovascular disease including patients with haemodynamically relevant unilateral renal artery stenosis.

Renal impairment
In patients with renal disease, thiazides may precipitate uraemia. Cumulative effects of the active substance may develop in patients with impaired renal function. If progressive renal impairment becomes evident, as indicated by a rising non-protein nitrogen, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy (see section 4.3).

Electrolyte imbalance
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). Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with ramipril may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing rapid diuresis, in patients who are receiving inadequate electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5). The first measurement of plasma potassium levels should be carried out during the first week following the start of treatment. If low potassium levels are detected, correction is required. Dilutional hyponatraemia may occur. Reduction in sodium levels can be initially asymptomatic and regular testing is therefore essential. Testing should be more frequent in elderly and cirrhotic patients. Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Serum potassium
ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalemia can occur. 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 section 4.5).

Hepatic Encephalopathy
Electrolyte disturbances due to diuretic therapy including hydrochlorothiazide may cause hepatic encephalopathy in patients with liver disease. Treatment should be immediately discontinued in case of hepatic encephalopathy.

Hypercalcaemia
Hydrochlorothiazide stimulates renal calcium reabsorption and may cause hypercalcaemia. It may interfere with test for parathyroid function.

Hypersensivity/angioedema
Angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8). In case of angioedema thiapril must be discontinued. Emergency therapy should be instituted promptly. Patient should be kept under observation for at least 12 to 24 hours and discharged after complete resolution of the symptoms. Intestinal angioedema has been reported in patients treated with ACE inhibitors including thiapril (see section 4.8). These patients presented with abdominal pain (with or without nausea or vomiting). The intestinal angioedema symptoms resolved after stopping the ACE inhibitor.
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 ramipril. Treatment with ramipril 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, 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.

Anaphylactic reactions during desensitization
The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom and other allergens are increased under ACE inhibition. A temporary discontinuation of /.../ should be considered prior to desensitization.

Neutropenia/agranulocytosis
Neutropenia/agranulocytosis have been rarely seen and bone marrow depression has also been reported. It is recommended to monitor the white blood cell count to permit detection of a possible leucopoenia. More frequent monitoring is advised in the initial phase of treatment and in patients with impaired renal function, those with concomitant collagen disease (e.g. lupus erythematosus or scleroderma), and all those treated with other medicinal products that can cause changes in the blood picture (see sections 4.5 and 4.8).

Acute Myopia and Angle-Closure Glaucoma
Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute 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 hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Ethnic differences
ACE inhibitors cause higher rate of angioedema in black patients than in non-black patients. As with other ACE inhibitors, ramipril may be less effective in lowering blood pressure in black people than in non black patients, possibly because of a higher prevalence of hypertension with low renin level in the black hypertensive population.

Athletes
Hydrochlorothiazide may produce a positive analytic result in the anti-doping test.

Metabolic and endocrine effects
Thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy. Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

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.

Other
Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

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). 6 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.

4.5 Interaction with other medicinal products and other forms of interaction

Contra-indicated combinations

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.
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).

Precautions for use

Potassium sparing diuretics and other plasma potassium increasing active substances (including Angiotensin II antagonists, trimethoprim, tacrolimus), potassium supplements or potassium-containing salt substitutes: Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with ramipril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when ramipril is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of ramipril with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

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

Antihypertensive agents (e.g. diuretics) and other substances that may decrease blood pressure (e.g. nitrates, tricyclic antidepressants, anaesthetics, acute alcohol intake, baclofen, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin): Potentiation of the risk of hypotension is to be anticipated (see section 4.2 for diuretics).

Vasopressor sympathomimetics and other substances (epinephrine) that may reduce the antihypertensive effect of ramipril: Blood pressure monitoring is recommended. Furthermore, the effect of the vasopressor sympathomimetics may be attenuated by hydrochlorothiazide.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood cell count: Increased likelihood of haematological reactions (see section 4.4).

Lithium salts: Excretion of lithium may be reduced by ACE inhibitors and therefore lithium toxicity may be increased. Lithium levels must be monitored. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. The combination of ramipril and hydrochlorothiazide with lithium is therefore not recommended.

Antidiabetic agents including insulin: Hypoglycaemic reactions may occur. Hydrochlorothiazide may 7 attenuate the effect of antidiabetic medicines. Particularly close blood glucose monitoring is therefore recommended in the initial phase of co-administration.

Nonsteroidal anti-inflammatory drugs and acetylsalicylic acid: Reduction of the antihypertensive effect of thiapril is to be anticipated. Furthermore, concomitant treatment of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and to an increase in kalaemia.

Oral anticoagulants: Anticoagulant effect may be decreased due to concomitant use of hydrochlorothiazide.

Corticosteroids, ACTH, amphotericin B, carbenoxolone, large amounts of liquorice, laxatives (in case of a prolonged use), and other kaliuretic or plasma potassium decreasing agents: Increased risk of hypokalaemia.

Digitalis preparations, active substances known to prolong the QT interval and antiarrhythmics: Their proarrhythmic toxicity may be increased or their antiarrhythmic effect decreased in the presence of electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia).

Methyldopa: Haemolysis possible.

Colestyramine or other enterally administered ion exchangers: Reduced absorption of hydrochlorothiazide. Sulphonamide diuretics should be taken at least one hour before or four to six hours after these medications.

Curare-type muscle relaxants: Possible intensification and prolongation of the muscular relaxing effect.

Calcium salts and plasma calcium increasing medicinal products: Rise in serum calcium concentration is to be anticipated in case of concomitant administration of hydrochlorothiazide; therefore close monitoring of serum calcium is required.

Carbamazepine: Risk of hyponatraemia due to additive effect with hydrochlorothiazide.

Iodine containing contrast media: In case of dehydration induced by diuretics including hydrochlorothiazide, there is increased risk of acute renal impairment, in particular when use of important doses of iodine containing contrast media.

Penicillin: Hydrochlorothiazide is excreted in the distal tubulus, and reduces excretion of penicillin.

Quinine: Hydrochlorothiazide reduces quinine excretion.

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

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

4.6 Pregnancy and lactation

Pregnancy:

Thiapril is not recommended during the first trimester of pregnancy (see section 4.4) and contraindicated during the second and third trimesters of pregnancy (see section 4.3).

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 anti-hypertensive treatments which have an established

safety profile for use in 8 pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started. ACE inhibitor/ Angiotensin II Receptor Antagonist (AIIRA) therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data'). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Newborns whose mothers have taken ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia (see also sections 4.3 and 4.4).

Hydrochlorothiazide, in cases of prolonged exposure during the third trimester of pregnancy, may cause a foeto-placental ischaemia and risk of growth retardation. Moreover, rare cases of hypoglycaemia and thrombocytopenia in neonates have been reported in case of exposure near term. Hydrochlorothiazide can reduce plasma volume as well as the uteroplacental blood flow.

Breastfeeding
Thiapril is contraindicated during breast-feeding.
Ramipril and hydrochlorothiazide are excreted in breast milk to such an extent that effects on the suckling child are likely if therapeutic doses of ramipril and hydrochlorothiazide are administered to breast-feeding women. Insufficient information is available regarding the use of ramipril during breast-feeding and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant. Hydrochlorothiazide is excreted in human milk. Thiazides during breast-feeding by lactating mothers have been associated with a decrease or even suppression of lactation. Hypersensitivity to sulphonamide-derived active substances, hypokalaemia and nuclear icterus might occur. Because of the potential for serious reactions in nursing infants from both active substances, a decision should be made whether to discontinue nursing or to discontinue therapy taking account of the importance of this therapy to the mother.

4.7 Effects on ability to drive and use machines

Some adverse effects (e.g. symptoms of a reduction in blood pressure such as dizziness) may impair the patient's ability to concentrate and react and, therefore, constitute a risk in situations where these abilities are of particular importance (e.g. operating a vehicle or machinery).

This can happen especially at the start of treatment, or when changing over from other preparations. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

4.8 Undesirable effects

The safety profile of ramipril includes persistent dry cough and reactions due to hypotension. Serious adverse reactions include angioedema, hyperkalaemia, renal or hepatic impairment, pancreatitis, severe skin reactions and neutropenia/agranulocytosis.

Adverse reactions frequency is defined using the following convention:

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).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

	Common	*Uncommon*	*Rare*	*Very rare*	*Not known*
Cardiac disorders		Myocardial ischaemia including angina pectoris or			

		myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral			
Blood and lymphatic system disorders		Eosinophilia	White blood cell count decreased (including neutropenia or agranulocytosis), red blood cell count decreased, haemoglobin decreased, platelet count decreased		Bone marrow failure, pancytopenia, haemolytic anaemia
Nervous system disorders	Headache, dizziness	Vertigo, paraesthesia, ageusia, dysgeusia,	Tremor, balance disorder		Cerebral ischaemia including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired, burning sensation, parosmia
Eye disorders		Visual disturbance including blurred vision	Conjunctivitis		
Ear and labyrinth disorders			Hearing impaired, tinnitus		
Respiratory, thoracic and mediastinal disorders	Non-productive tickling cough, bronchitis, sinusitis, dyspnoea	Bronchospasm including asthma aggravated, nasal congestion			
Gastrointestinal disorders	Gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting	Pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, constipation, dry mouth	Glossitis		Aphtous stomatitis
Renal and urinary disorders		Renal impairment including renal failure acute,			

		urine output increased, worsening of a pre-existing proteinuria, blood urea increased, blood creatinine increased			
Skin and subcutaneous tissue disorders	Rash in particular maculo-papular	Angioedema; very exceptionally, the airway obstruction resulting from angioedema may have a fatal outcome; pruritus, hyperhidrosis	Exfoliative dermatitis, urticaria, onycholysis,	Photosensitivity reaction	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia
Musculoskeletal and connective tissue disorders	Muscle spasms, myalgia	Arthralgia			
Endocrine disorders					Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Blood potassium increased	Anorexia, decreased appetite,			Blood sodium decreased
Vascular disorders	Hypotension, orthostatic blood pressure decreased, syncope	Flushing	Vascular stenosis, hypoperfusion, vasculitis		Raynaud's phenomenon
General disorders and administration site conditions	Chest pain, fatigue	Pyrexia	Asthenia		
Immune system disorders					Anaphylactic or anaphylactoid reactions, antinuclear antibody increased
Hepatobiliary disorders		Hepatic enzymes and/or bilirubin conjugated increased,	Jaundice cholestatic, hepatocellular damage		Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional).

Reproductive system and breast disorders		Transient erectile impotence, libido decreased			Gynaecomastia
Psychiatric disorders		Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence	Confusional state		Disturbance in attention

Paediatric Population

The safety of ramipril was monitored in 325 children and adolescents, aged 2-16 years old during 2 clinical trials. Whilst the nature and severity of the adverse events are similar to that of the adults, the frequency of the following is higher in the children:

• Tachycardia, nasal congestion and rhinitis, "common" (i.e. ≥ 1/100 to < 1/10) in paediatric, and "uncommon" (i.e. ≥ 1/1,000 to < 1/100) in adult population.

• Conjunctivitis "common" (i.e. ≥ 1/100 to < 1/10) in paediatric while "rare" (i.e. ≥ 1/10,000 to < 1/1,000) in adult population.

• Tremor and urticaria "uncommon" (i.e. ≥ 1/1,000 to < 1/100) in paediatric population while "rare" (i.e. ≥ 1/10,000 to < 1/1,000) in adult population.

The overall safety profile for ramipril in paediatric patients does not differ significantly from the safety profile in adults.

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 the national reporting system.

4.9 Overdose

Symptoms associated with overdosage of ACE inhibitors may include excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure. The patient should be closely monitored and the treatment should be symptomatic and supportive. Suggested measures include primary detoxification (gastric lavage, administration of adsorbents) and measures to restore haemodynamic stability, including, administration of alpha 1 adrenergic agonists or angiotensin II (angiotensinamide) administration. Ramiprilat, the active metabolite of ramipril is poorly removed from the general circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE Inhibitors and diuretics, ATC code C09BA05.

Mechanism of action

Remipril

Ramiprilat, the active metabolite of the prodrug ramipril, inhibits the enzyme dipeptidylcarboxypeptidase I (synonyms: angiotensin-converting enzyme; kininase II). In plasma and tissue this enzyme catalyses the conversion of angiotensin I to the active

vasoconstrictor substance angiotensin II, as well as the breakdown of the active vasodilator bradykinin. Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilatation.

Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in aldosterone secretion. The average response to ACE inhibitor monotherapy was lower in black (Afro-Caribbean) hypertensive patients (usually a low-renin hypertensive population) than in non-black patients.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. The mechanism of antihypertensive effect of thiazide diuretics is not fully known. It inhibits the reabsorption of sodium and chloride in the distal tubule. The increased renal excretion of these ions is accompanied by increased urine output (due to osmotic binding of water). Potassium and magnesium excretion are increased, uric acid excretion is decreased. Possible mechanisms of the antihypertensive action of hydrochlorothiazide could be: the modified sodium balance, the reduction in extracellular water and plasma volume, a change in renal vascular resistance as well as a reduced response to norepinephrine and angiotensin II

Pharmacodynamic effects

Ramipril

Administration of ramipril causes a marked reduction in peripheral arterial resistance. Generally, there are no major changes in renal plasma flow and glomerular filtration rate. Administration of ramipril to patients with hypertension leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate. In most patients the onset of the antihypertensive effect of a single dose becomes apparent 1 to 2 hours after oral administration. The peak effect of a single dose is usually reached 3 to 6 hours after oral administration. The antihypertensive effect of a single dose usually lasts for 24 hours. The maximum antihypertensive effect of continued treatment with ramipril is generally apparent after 3 to 4 weeks. It has been shown that the antihypertensive effect is sustained under long term therapy lasting 2 years. Abrupt discontinuation of ramipril does not produce a rapid and excessive rebound increase in blood pressure. 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.

Hydrochlorothiazide

With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6 to 12 hours. The onset of the antihypertensive effect occurs after 3 to 4 days and can last up to one week after discontinuation of therapy. The

blood-pressure-lowering effect is accompanied by slight increases in the filtration fraction, renal vascular resistance and plasma renin activity.

Concomitant administration of ramipril-hydrochlorothiazide

In clinical trials, the combination led to greater reductions in blood pressure than when either of the products was administered alone. Presumably through blockade of the renin-angiotensin-aldosterone system, coadministration of ramipril to hydrochlorothiazide tends to reverse the potassium loss associated with these diuretics. 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.

Paediatric Population

Ramipril

In a randomized, double-blind, placebo-controlled clinical study involving 244 paediatric patients with hypertension (73% primary hypertension), aged 6-16 years, patients received either low dose, medium dose or high dose of ramipril to achieve plasma concentrations of ramiprilat corresponding to the adult dose range of 1.25 mg, 5 mg and 20 mg on the basis of body weight. At the end of 4 weeks, ramipril was ineffective in the endpoint of lowering systolic blood pressure but lowered diastolic blood pressure at the highest dose. Both medium and high doses of Ramipril showed significant reduction of both systolic and diastolic BP in children with confirmed hypertension.

This effect was not seen in a 4 week dose-escalation, randomized, double-blind withdrawal study in 218 paediatric patients aged 6-16 years (75% primary hypertension), where both diastolic and systolic blood pressures demonstrated a modest rebound but not a statistically significant return to the baseline, in all three dose levels tested (low dose (0.625 mg – 2.5 mg), medium dose (2.5 mg – 10 mg) or high dose (5mg – 20 mg) ramipril based on weight. Ramipril did not have a linear dose response in the paediatric population studied.

5.2 Pharmacokinetic properties

Pharmacokinetics and Metabolism

Ramipril

Absorption

Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations of ramipril are reached within one hour. Based on urinary recovery, the extent of absorption is at least 56 % and is not significantly influenced by the presence of food in the gastrointestinal tract. The bioavailability of the active metabolite ramiprilat after oral administration of 2.5 mg and 5 mg ramipril is 45 %.

Peak plasma concentrations of ramiprilat, the sole active metabolite of ramipril are reached 2-4 hours after ramipril intake. Steady-state plasma concentrations of ramiprilat after once daily dosing with the usual doses of ramipril are reached by about the fourth day of treatment.

Distribution

The serum protein binding of ramipril is about 73 % and that of ramiprilat about 56 %.

Biotransformation

Ramipril is almost completely metabolised to ramiprilat, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat.

Elimination

Excretion of the metabolites is primarily renal. Plasma concentrations of ramiprilat decline in a polyphasic manner. Because of its potent, saturable binding to ACE and slow dissociation from the enzyme, ramiprilat shows a prolonged terminal elimination phase at very low plasma concentrations. After multiple once-daily doses of ramipril, the effective half-life of ramiprilat concentrations was 1317 hours for the 5-10 mg doses and longer for the lower 1.25-2.5 mg doses. This difference is related to the saturable capacity of the enzyme to bind ramiprilat. A single oral dose of ramipril produced an undetectable level of ramipril and its metabolites in breast milk. However, the effect of multiple doses is not known.

Patients with renal impairment (see section 4.2)

Renal excretion of ramiprilat is reduced in patients with impaired renal function, and renal ramiprilat clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of ramiprilat, which decrease more slowly than in subjects with normal renal function. Patients with liver impairment (see section 4.2)

In patients with impaired liver function, the metabolism of ramipril to ramiprilat was delayed due to diminished activity of hepatic esterases, and plasma ramipril levels in these patients were increased. Peak concentrations of ramiprilat in these patients, however, are not different from those seen in subjects with normal hepatic function.

Hydrochlorothiazide

Absorption

Following oral administration about 70 % of hydrochlorothiazide is absorbed from the gastrointestinal tract. Peak plasma concentrations of hydrochlorothiazide are reached within 1.5 to 5 hours.

Distribution

The plasma protein binding of hydrochlorothiazide is 40 %.

Biotransformation

Hydrochlorothiazide undergoes negligible hepatic metabolism.

Elimination

Hydrochlorothiazide is eliminated almost completely (> 95 %) in an unchanged form through the kidneys; 50 to 70 % of a single oral dose is eliminated within 24 hours. The elimination half-life is 5 to 6 hours.

Patients with renal impairment (see section 4.2)

Renal excretion of hydrochlorothiazide is reduced in patients with impaired renal function, and renal hydrochlorothiazide clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of hydrochlorothiazide, which decrease more slowly than in subjects with normal renal function.

Patients with liver impairment (see section 4.2)

In patients with hepatic cirrhosis the pharmacokinetics of hydrochlorothiazide has not changed significantly. The pharmacokinetics of hydrochlorothiazide has not been studied in patients with cardiac failure.

Ramipril and Hydrochlorothiazide

The concurrent administration of ramipril and hydrochlorothiazide does not affect their bioavailability. The combination product can be considered as bioequivalent to products containing the individual components.

Paediatric Population

Ramipril

The pharmacokinetic profile of ramipril was studied in 30 paediatric hypertensive patients, aged 2-16 years, weighing >10 kg. After doses of 0.05 to 0.2 mg/kg, ramipril was rapidly and extensively metabolized to ramiprilat. Peak plasma concentrations of ramiprilat occurred within 2-3 hours. Ramiprilat clearance highly correlated with the log of body weight ($p<0.01$) as well as dose ($p<0.001$). clearance and volume of distribution increased with increasing children age for each dose group. The dose of 0.05 mg /kg in children achieved exposure levels comparable to those in adults treated with ramipril 5mg. The dose of 0.2 mg/kg in children resulted in exposure levels higher than the maximum recommended dose of 10 mg per day in adults.

5.3 Preclinical safety data

Ramipril
Irreversible kidney damage has been observed in very young rats given a single dose of ramipril.

Ramipril and Hydrochlorothiazide
In rats and mice the combination of ramipril and hydrochlorothiazide has no acute toxic activity up to 10,000 mg/kg. Repeated doses administration studies performed in rats and monkeys revealed only disturbances in electrolytes balance.
No studies on mutagenicity and carcinogenicity have been performed with the combination as studies with individual components showed no risk. Reproduction studies in rats and rabbits revealed that the combination is somewhat more toxic than either of the single components but none of the studies revealed a teratogenic effect of the combination.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Sodium starch glycolate
Microcrystalline cellulose
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25˚ C. store in the original package in order to protect from moisture.

6.5 NATURE AND CONTENT OF CONTAINER:

3 x 10 tablets are packed in an aluminum blister strips along with a leaflet in a printed carton. This is duly labelled and strapped.

6.6 SPECIAL PRECAUTION FOR DISPOSAL:

To be destroyed by NAFDAC enforcement unit

7. <APPLICANT/SUPPLIER>

May & Baker Nigeria Plc.
1 May & Baker Avenue, Off Idiroko, Opposite covenant
University Ota, Ogun State.

8. WHO PREQUALIFICATION REFERENCE NUMBER

9. DATE OF <PREQUALIFICATION> / <RENEWAL OF PREQUALIFICATION>

10. DATE OF REVISION OF THE TEXT

23/10/2019