Public Assessment Report

Decentralised Procedure

Ramipril/Hydrochlorothiazide Ranbaxy 2.5 mg/12.5 mg and 5 mg/25 mg Tablets

Applicant: Ranbaxy (UK) Limited

Italian Marketing Authorisation Number: 042745

European procedure number: IT/H/0313/001-002/DC

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Module 1

Information about the Initial Procedure

Product Name	**IT/H/0313/001/DC:** Ramipril/Hydrochlorothiazide Ranbaxy 2.5 mg/12.5 mg Tablets **IT/H/0313/002/DC:** Ramipril/Hydrochlorothiazide Ranbaxy 5 mg/25 mg Tablets
Type of application	Generic, Article 10 (1)
Active Substance	Ramipril/Hydrochlorotiazide
Form	Tablets
Strength	2.5 mg/12.5 mg, 5 mg/25 mg,
MA Holder	Ranbaxy (UK) Limited Building 4, Chiswick Park, 566 Chiswick High Road, London, W45YE, United Kingdom
Reference Member State (RMS)	IT
Concerned Memember States (CMS)	CZ, DE, ES and PL
Procedure number	IT/H/0313/001-002/DC
Timetable	End of procedure: Day 180 - 14 January 2014

Module 2

Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Italian version of the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level would be available on the AIFA website once the marketing Authorization will be granted.

Here is reported the English version of the SMPC approved at European level.

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ramipril / Hydrochlorothiazide Ranbaxy 2.5 mg / 12.5 mg Tablets
Ramipril / Hydrochlorothiazide Ranbaxy 5 mg / 25 mg Tablets

[To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ramipril / Hydrochlorothiazide Ranbaxy 2.5 mg / 12.5 mg Tablets
Each tablet contains ramipril 2.5 mg and hydrochlorothiazide 12.5 mg.

Ramipril / Hydrochlorothiazide Ranbaxy 5 mg / 25 mg Tablets
Each tablet contains ramipril 5 mg and hydrochlorothiazide 25 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Ramipril / Hydrochlorothiazide Ranbaxy 2.5 mg / 12.5 mg: White to off white oblong shaped tablets with ‘R’ and ‘21’ on either side of score line on one side and score line on other side.

The score line is not intended for breaking the tablet.

Ramipril / Hydrochlorothiazide Ranbaxy 5 mg / 25 mg: White to off white oblong shaped tablets with ‘R’ and ‘22’ on either side of score line on one side and score line on other side.

The tablet can be divided into equal doses.

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

Oral use.
It is recommended that Ramipril + Hydrochlorothiazide Ranbaxy is taken once daily, at the same time of the day, usually in the morning.

Ramipril / Hydrochlorothiazide Ranbaxy can be taken before, with or after meals, because food intake does not modify its bioavailability (see section 5.2).

Ramipril / Hydrochlorothiazide Ranbaxy has to be swallowed with liquid. It must not be chewed or crushed.

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.

Ramipril + Hydrochlorothiazide Ranbaxy 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 Ramipril + Hydrochlorothiazide Ranbaxy.

Patients with renal impairment
Ramipril + Hydrochlorothiazide Ranbaxy 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 Ramipril + Hydrochlorothiazide Ranbaxy. 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 Ramipril + Hydrochlorothiazide Ranbaxy 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.

Ramipril + Hydrochlorothiazide Ranbaxy is contraindicated in severe hepatic impairment (see section 4.3).

Elderly
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
Ramipril + Hydrochlorothiazide Ranbaxy is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy.

4.3 Contraindications

- Hypersensitivity to the active substance or to any other ACE (Angiotensin Converting Enzyme) inhibitor, hydrochlorothiazide, other thiazide diuretics, sulfonamides or any of the excipients of Ramipril + Hydrochlorothiazide Ranbaxy (see 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 Ramipril + Hydrochlorothiazide Ranbaxy (see section 4.4)
- Severe impairment of liver function, hepatic encephalopathy

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.

- *Elderly patients*

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 4.2). There is a risk of impairment of renal function, particularly in patients with congestive heart failure or after renal transplant..

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.

Hyperkalaemia

Hyperkalaemia has been observed in some patients treated with ACE inhibitors including Ramipril + Hydrochlorothiazide Ranbaxy. Patients at risk for development of hyperkalaemia include those with renal insufficiency, age (> 70 years), uncontrolled diabetes mellitus, or those using potassium salts, potassium retaining diuretics and other plasma potassium increasing active substances or conditions such as dehydration, acute cardiac decompensation, metabolic acidosis. If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (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.

Angioedema
Angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8).

In case of angioedema Ramipril + Hydrochlorothiazide Ranbaxy 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 Ramipril + Hydrochlorothiazide Ranbaxy (see section 4.8). These patients presented with abdominal pain (with or without nausea or vomiting).

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 Ramipril + Hydrochlorothiazide Ranbaxy 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).

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.

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.

Precautions for use

Potassium salts, heparin, potassium-retaining diuretics and other plasma potassium increasing active substances (including Angiotensin II antagonists, trimethoprim, tacrolimus, ciclosporin): Hyperkalaemia may occur; therefore close monitoring of serum potassium is required.

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.

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 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 Ramipril + Hydrochlorothiazide Ranbaxy 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.

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Ramipril + Hydrochlorothiazide Ranbaxy 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 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

Ramipril + Hydrochlorothiazide Ranbaxy 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 + hydrochlorothiazide includes adverse reactions occurring in the context of hypotension and/or fluid depletion due to increased diuresis. The ramipril active substance may induce persistent dry cough, while the hydrochlorothiazide active substance may lead to worsening of glucose, lipid and uric acid metabolism. The two active substances have inverse effects on plasma potassium. Serious adverse reactions include angioedema or anaphylactic reaction, 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	Very rare	Not known
Cardiac disorders		Myocardial ischaemia including angina pectoris, tachycardia, arrhythmia, palpitations, oedema peripheral		Myocardial infarction
Blood and lymphatic system disorders		White blood cell count decreased, red blood cell count decreased, haemoglobin decreased, haemolytic anaemia, platelet count decreased		Bone marrow failure, neutropenia including agranulocytosis, pancytopenia, eosinophilia Haemoconcentration in the context of fluid depletion
Nervous system disorders	Headache, dizziness	Vertigo, paraesthesia, tremor, balance disorder, burning sensation, dysgeusia, ageusia		Cerebral ischaemia including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired, parosmia
Eye disorders		Visual disturbance		Xanthopsia,

		including blurred vision, conjunctivitis		lacrimation decreased due to hydrochlorothiazide
Ear and labyrinth disorders		Tinnitus		Hearing impaired
Respiratory, thoracic and mediastinal disorders	Non-productive tickling cough, bronchitis	Sinusitis, dyspnoea, nasal congestion		Bronchospasm including asthma aggravated Alveolitis allergic, non cardiogenic pulmonary oedema due to hydrochlorothiazide
Gastrointestinal disorders		Gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, gastritis, nausea, constipation Gingivitis due to hydrochlorothiazide	Vomiting, aphtous stomatitis, glossitis, diarrhoea, abdominal pain upper, dry mouth	Pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema Sialoadenitis due to hydrochlorothiazide
Renal and urinary disorders		Renal impairment including renal failure acute, urine output increased, blood urea increased, blood creatinine increased		Worsening of a pre-existing proteinuria Interstitial nephritis due to hydrochlorothiazide
Skin and subcutaneous tissue disorders		Angioedema: very exceptionally, the airway obstruction resulting from angioedema may have a fatal outcome; dermatitis psoriasiform, hyperhidrosis, rash, in particular maculo-papular, pruritus, alopecia		Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, exfoliative dermatitis, photosensitivity reaction, onycholysis, pemphigoid or lichenoid exanthema or enanthema, urticaria Systemic lupus erythematosus due to hydrochlorothiazide
Musculoskeletal and connective tissue disorders		Myalgia		Arthralgia, muscle spasms

				Muscular weakness, musculoskeletal stiffness, tetany due to hydrochlorothiazide
Metabolism and nutrition disorders	Diabetes mellitus inadequate control, glucose tolerance decreased, blood glucose increased, blood uric acid increased, gout aggravated, blood cholesterol and/or triglycerides increased due to hydrochlorothiazide	Anorexia, decreased appetite Blood potassium decreased, thirst due to hydrochlorothiazide	Blood potassium increased due to ramipril	Blood sodium decreased Glycosuria, metabolic alkalosis, hypochloraemia, hypomagnesaemia, hypercalcaemia, dehydration due to hydrochlorothiazide
Vascular disorders		Hypotension, orthostatic blood pressure decreased, syncope, flushing		Thrombosis in the context of severe fluid depletion, vascular stenosis, hypoperfusion, Raynaud's phenomenon, vasculitis
General disorders and administration site conditions	Fatigue, asthenia	Chest pain, pyrexia		
Immune system disorders				Anaphylactic or anaphylactoid reactions to either ramipril or anaphylactic reaction to hydrochlorothiazide, antinuclear antibody increased
Hepatobiliary disorders		Cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional), hepatic enzyme and /or bilirubin conjugated increased Calculous cholecystitis due to hydrochlorothiazide		Acute hepatic failure, jaundice cholestatic, hepatocellular damage
Reproductive		Transient erectile		Libido decreased,

system and breast disorders		impotence		gynaecomastia
Psychiatric disorders		Depressed mood, apathy, anxiety, nervousness, sleep disorders including somnolence		Confusional state, restlessness, disturbance in attention

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 listed in Appendix V

4.9 Overdose

Symptoms associated with overdosage of ACE inhibitors may include excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, renal failure, cardiac arrhythmia, impairment of consciousness including coma, cerebral convulsions, pareses, and paralytic ileus.

In predisposed patients (e.g. prostatic hyperplasia) hydrochlorothiazide overdose may induce acute urinary retention.

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: ramipril and diuretics, ATC code C09BA05

Mechanism of action

Ramipril

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.

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, co-administration 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.

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 13-17 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.

5.3 Preclinical safety data

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

Hypromellose (E464)

Microcrystalline cellulose (E460)
Pregelatinised starch (Maize)
Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25ºC.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Dessicant Embedded Cold form blister pack (OPA/Alu/PE/HDPE-Alu), , Comprises of cold form laminate composed of soft tempered, plain aluminium foil laminated to polyamide film on one side and other side is extrusion coated with desiccant embedded polyethylene having a
layer of HDPE.

Triplex blister pack (PVC/PE/PVdC-Alu)
14/20/28/50/100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Module 3

Package Leaflets

In accordance with Directive 2010/84/EU, the Italian version of the package leaflet for products granted Marketing Authorisations at a national level would be available on the AIFA website once the marketing Authorization will be granted.

Here is reported the English version of the PIL approved at European level.

1.3.1 Package leaflet: Information for the user

Ramipril / Hydrochlorothiazide Ranbaxy 2.5 mg / 12.5 mg Tablets
Ramipril / Hydrochlorothiazide Ranbaxy 5 mg / 25 mg Tablets
[To be completed nationally]

Ramipril / Hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Ramipril / Hydrochlorothiazide Ranbaxy is and what it is used for

Ramipril / Hydrochlorothiazide Ranbaxy is a combination of two medicines called ramipril and hydrochlorothiazide.

Ramipril belongs to a group of medicines called “ACE inhibitors” (Angiotensin Converting Enzyme Inhibitors). It works by:
- Decreasing your body’s production of substances that raise your blood pressure
- Making your blood vessels relax and widen
- Making it easier for your heart to pump blood around your body.

Hydrochlorothiazide belongs to a group of medicines called “thiazide diuretics” or water tablets. It works by increasing the amount of water (urine) you produce. This lowers your blood pressure.

Ramipril / Hydrochlorothiazide Ranbaxy is used to treat high blood pressure. The two active substances work together to lower your blood pressure. They are used together when treatment with just one did not work.

2. What you need to know before you take Ramipril / Hydrochlorothiazide Ranbaxy

Do not take Ramipril / Hydrochlorothiazide Ranbaxy:

- If you are allergic to ramipril, hydrochlorothiazide or any of the other ingredients of this medicine (listed in section 6)
- If you are allergic (hypersensitive) to medicines similar to Ramipril + Hydrochlorothiazide Ranbaxy (other ACE inhibitors or sulphonamide derived medicines).
- Signs of an allergic reaction may include a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue
- If you have ever had a serious allergic reaction called “angioedema”. The signs include itching, hives (urticaria), red marks on the hands, feet and throat, swelling of the throat and tongue, swelling around the eyes and lips, difficulty breathing and swallowing
- If you are having dialysis or any other type of blood filtration. Depending on the machine that is used, Ramipril + Hydrochlorothiazide Ranbaxy may not be suitable for you
- If you have severe liver problems
- If you have abnormal amounts of salt substances (calcium, potassium, sodium) in your blood
- If you have kidney problems where the blood supply to your kidney is reduced (renal artery stenosis)
- During the last 6 months of pregnancy (see section below on “Pregnancy and breast-feeding”)
- If you are breast-feeding (see section below on “Pregnancy and breast-feeding”).

Do not take Ramipril / Hydrochlorothiazide Ranbaxy if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Ramipril + Hydrochlorothiazide Ranbaxy.

Warnings and precautions

Talk to your doctor or pharmacist before taking Ramipril / Hydrochlorothiazide Ranbaxy:

- If you have heart, liver or kidney problems
- If you have lost a lot of body salts or fluids (through being sick (vomiting), having diarrhoea, sweating more than usual, being on a low salt diet, taking diuretics (water tablets) for a long time or having had dialysis)
- If you are going to have treatment to reduce your allergy to bee or wasp stings (desensitization)

- If you are going to receive an anaesthestic. This may be given for an operation or any dental work. You may need to stop your Ramipril + Hydrochlorothiazide Ranbaxy treatment one day beforehand; ask your doctor for advice
- If you have high amounts of potassium in your blood (shown in blood test results)
- If you have a collagen vascular disease such as scleroderma or systemic lupus erythematosus
- You must tell your doctor if you think that you are (or might become) pregnant. Ramipril + Hydrochlorothiazide Ranbaxy is not recommended in the first 3 months of pregnancy and may cause serious harm to your baby after 3 months of pregnancy (see section below on "Pregnancy and breast-feeding").

Children and adolescents

Ramipril / Hydrochlorothiazide Ranbaxy is not recommended for children and young people under the age of 18 years. This is because the drug has never been used in these age groups.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Ramipril / Hydrochlorothiazide Ranbaxy.

Other medicines and Ramipril / Hydrochlorothiazide Ranbaxy

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Please tell your doctor if you are taking any of the following medicines. They can make Ramipril / Hydrochlorothiazide Ranbaxy work less well:

- Medicines used to relieve pain and inflammation (e.g. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen or indometacin and aspirin)
- Medicines used for the treatment of low blood pressure, shock, cardiac failure, asthma or allergies such as ephedrine, noradrenaline or adrenaline. Your doctor will need to check your blood pressure.

Please tell your doctor if you are taking any of the following medicines. They can increase the chance of getting side effects if you take them with Ramipril / Hydrochlorothiazide Ranbaxy:

- Medicines used to relieve pain and inflammation (e.g. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen or indometacin and aspirin)
- Medicines which can lower the amount of potassium in your blood. These include medicines for constipation, diuretics (water tablets), amphotericin B (used for fungal infections) and ACTH (used to test if your adrenal glands are working properly)
- Medicines for cancer (chemotherapy)
- Medicines for heart problems, including problems with your heartbeat
- Medicines to stop the rejection of organs after a transplant such as ciclosporin
- Diuretics (water tablets) such as furosemide
- Medicines which can increase the amount of potassium in your blood such as spironolactone, triamterene, amiloride, potassium salts, and heparin (for thinning blood)
- Steroid medicines for inflammation such as prednisolone

- Calcium supplements
- Allopurinol (used to lower the uric acid in your blood)
- Procainamide (for heart rhythm problems)
- Colestyramine (for reducing fat amounts in your blood)
- Carbamazepine (for epilepsy)

Please tell your doctor if you are taking any of the following medicines. They may be affected by Ramipril / Hydrochlorothiazide Ranbaxy:

- Medicines for diabetes such as oral glucose lowering medicines and insulin. Ramipril / Hydrochlorothiazide Ranbaxy may lower your blood sugar amounts. Check your blood sugar amounts closely while taking Ramipril / Hydrochlorothiazide Ranbaxy
- Lithium (for mental health problems). Ramipril / Hydrochlorothiazide Ranbaxy may increase
  the amount of lithium in your blood. Your lithium amount will need to be closely checked by your doctor
- Medicines to relax your muscles
- Quinine (for malaria)
- Medicines that contain iodine, these may be used when you are having a scan or X-ray in hospital
- Penicillin (for infections)
- Medicines to thin the blood that you take by mouth (oral anticoagulants) such as warfarin.

If any of the above apply to you (or you are not sure), talk to your doctor before taking Ramipril / Hydrochlorothiazide Ranbaxy.

Tests

Check with your doctor or pharmacist before taking your medicine:
- If you are having a test for parathyroid function. Ramipril / Hydrochlorothiazide Ranbaxy might affect the results of the test
- If you are sports person having an anti-doping test. Ramipril / Hydrochlorothiazide Ranbaxy might give you a positive result.

Ramipril / Hydrochlorothiazide Ranbaxy with food and alcohol

- Drinking alcohol with Ramipril / Hydrochlorothiazide Ranbaxy may make you feel dizzy or light-headed. If you are concerned about how much you can drink while you are taking Ramipril / Hydrochlorothiazide Ranbaxy, discuss this with your doctor as medicines used to reduce blood pressure and alcohol can have additive effects.
- Ramipril / Hydrochlorothiazide Ranbaxy may be taken with or without food.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine

You must tell your doctor if you think that you are (or might become) pregnant.

You should not take Ramipril / Hydrochlorothiazide Ranbaxy in the first 12 weeks of pregnancy, and you must not take them at all after the 13th week as their use during pregnancy may possibly be harmful to the baby.

If you become pregnant while on Ramipril / Hydrochlorothiazide Ranbaxy, tell your doctor immediately. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.

You should not take Ramipril / Hydrochlorothiazide Ranbaxy if you are breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

You may feel dizzy, while taking Ramipril / Hydrochlorothiazide Ranbaxy. This is more likely to happen when you start taking Ramipril / Hydrochlorothiazide Ranbaxy or start taking a higher dose. If this happens, do not drive or use any tools or machines.

3. How to take Ramipril / Hydrochlorothiazide Ranbaxy

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Taking this medicine

- Take this medicine by mouth at the same time of day each day, usually in the morning.
- Swallow the tablets with liquid.
- Do not crush or chew the tablets.
  The score line is not intended for breaking the tablet.

How much to take

Treatment of high blood pressure
Your doctor will adjust the amount you take until your blood pressure is controlled.

Elderly
Your doctor will reduce the initial dose and adjust your treatment more slowly.

If you take more Ramipril / Hydrochlorothiazide Ranbaxy than you should

Tell a doctor or go to the nearest hospital casualty department straight away. Do not drive to the hospital, get somebody else to take you or call for an ambulance. Take the medicine pack with you. This is so the doctor knows what you have taken.

If you forget to take Ramipril / Hydrochlorothiazide Ranbaxy

- If you miss a dose, take your normal dose when it is next due.
- Do not take a double dose to make up for a forgotten tablet.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Ramipril / Hydrochlorothiazide Ranbaxy and see a doctor straight away, if you notice any of the following serious side effects - you may need urgent medical treatment:

- Swelling of the face, lips or throat which make it difficult to swallow or breathe, as well as itching and rashes. This could be a sign of a severe allergic reaction to Ramipril + Hydrochlorothiazide Ranbaxy
- Severe skin reactions including rash, ulcers in your mouth, worsening of a pre-existing skin disease, reddening, blistering or detachment of skin (such as Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiform).

Tell your doctor immediately if you experience:

- Faster heart rate, uneven or forceful heartbeat (palpitations), chest pain, tightness in your chest or more serious problems including heart attack and stroke
- Shortness of breath, cough fever lasting 2 to 3 days and feeling less hungry. These could be signs of lung problems including inflammation
- Bruising more easily, bleeding for longer than normal, any sign of bleeding (e.g. bleeding from the gums), purple spots, blotching on the skin or getting infections more easily than usual, sore throat and fever, feeling tired, faint, dizzy or having pale skin. These can be signs of blood or bone marrow problems.
- Severe stomach pain which may reach through to your back. This could be a sign of pancreatitis (inflammation of the pancreas)
- Fever, chills, tiredness, loss of appetite, stomach pain, feeling sick, yellowing of your skin or eyes (jaundice). These can be signs of liver problems such as hepatitis (inflammation of the liver) or liver damage.

Other side effects include:

Please tell your doctor if any of the following gets serious or lasts longer than a few days.
Common (affects less than 1 in 10 people)

- Headache, feeling week or tired
- Feeling dizzy. This is more likely to happen when you start taking Ramipril + Hydrochlorothiazide Ranbaxy or start taking a higher dose
- Dry tickly cough or bronchitis
- Blood test showing a higher amount of sugar than usual in your blood. If you have diabetes, this may make your diabetes worse
- Blood test showing a higher amount of uric acid or more fat than usual in your blood

- Painful, red, and swollen joints

Uncommon (affects less than 1 in 100 people)

- Skin rash with or without raised area
- Flushing, fainting, hypotension (abnormally low blood pressure), especially when you stand or sit up quickly
- Balance problems (vertigo)
- Itching and unusual skin sensations such as numbness, tingling, pricking, burning or creeping on your skin (paraesthesia)
- Loss or change in the way things taste
- Sleep problems
- Feeling depressed, anxious, more nervous or shaky than usual
- Blocked nose, inflammation of your sinuses (sinusitis), shortness of breath
- Inflammation of the gums (gingivitis), swollen mouth
- Red, itchy, swollen or watery eyes
- Ringing in your ears
- Blurred vision
- Hair loss
- Chest pain
- Pain in your muscles
- Constipation, stomach or gut pain
- Indigestion or feeling sick
- Passing more water (urine) than usual over the day
- Sweating more than usual or feeling thirsty
- Loss or decrease of appetite (anorexia), feeling less hungry
- Increased or irregular heartbeat
- Swollen arms and legs. This may be a sign of your body holding onto more water than usual
- Fever
- Sexual inability in men
- Blood tests showing a decrease in the number of red blood cells, white blood cells or platelets or in the amount of haemoglobin
- Blood tests showing changes in the way your liver, pancreas or kidneys are working
- Blood tests showing less potassium than usual in your blood.

Very rare (affects less than 1 in 10,000 people)

- Being sick, getting diarrhoea or heartburn
- Red swollen tongue or dry mouth
- Blood tests showing more potassium than usual in your blood.

Other side effects reported:

Please tell your doctor if any of the following gets serious or lasts longer than a few days.

- Difficulty concentrating, feeling restless or confused
- Fingers and toes changing colour when cold and then tingling or painful when you warm up. This could be Raynaud's phenomenon

- Breast enlargement in men
- Blood clots
- Disturbed hearing
- Your eyes watering less than usual
- Objects looking yellow
- Dehydration
- Swelling, pain and redness in your cheek (inflammation of a salivary gland)
- A swelling in your gut called “intestinal angioedema” presenting with symptoms like abdominal pain, vomiting and diarrhoea
- Being more sensitive to the sun than usual
- Severe flaking or peeling of the skin, itchy, lumpy rash or other skin reactions such as red rash on your face or forehead
- Skin rash or bruising
- Blotches on your skin and cold extremities
- Nail problems (e.g. loosening or separation of a nail from its bed)
- Musculoskeletal rigidity or not being able to move your jaw (tetany)
- Weakness or cramps in your muscles
- Reduced sexual desire in men or women
- Blood in your water (urine). This could be a sign of a kidney problem (interstitial nephritis)
- More sugar than usual in your water (urine)
- An increased number of certain white blood cells (eosinophilia) found during a blood test
- Blood tests showing too few blood cells in your blood (pancytopenia)
- Blood tests showing a change in the amount of salts such as sodium, calcium, magnesium and chloride in your blood
- Slowed or impaired reactions
- Change in the way things smell
- Difficulty breathing or worsening of asthma

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. by reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ramipril / Hydrochlorothiazide Ranbaxy

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store below 25ºC.

Store in the original package in order to protect from moisture.

Do not throw away any medicine via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ramipril / Hydrochlorothiazide Ranbaxy contains

- The active substances are ramipril and hydrochlorothiazide.
    - Each tablet contains ramipril 2.5 mg and hydrochlorothiazide 12.5 mg.
    - Each tablet contains ramipril 5 mg and hydrochlorothiazide 25 mg.

- The other ingredients are hypromellose, microcrystalline cellulose, pregelatinised starch, (Maize) sodium stearyl fumarate.

What Ramipril / Hydrochlorothiazide Ranbaxy looks like and contents of the pack

- Ramipril / Hydrochlorothiazide Ranbaxy 2.5 mg + 12.5 mg: White to off white oblong shaped tablets with 'R' and '21' on either side of score line on one side and score line on other side. The score line is not intended for breaking the tablet.

- Ramipril / Hydrochlorothiazide Ranbaxy 5 mg + 25 mg: White to off white oblong shaped tablets with 'R' and '22' on either side of score line on one side and score line on other side. The tablet can be divided into equal doses.

Ramipril / Hydrochlorothiazide Ranbaxy are available in packs of 14, 20, 28, 50 & 100 tablets in Dessicant Embedded Cold form blister pack (OPA/Alu/PE/HDPE) & Triplex blister pack (PVC/PE/PVdC/Alu).

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

{Name of the Member State} > < {Name of the medicinal product}

{Name of the Member State} > < {Name of the medicinal product}

This leaflet was last approved in {MM/YYYY}

[To be completed nationally]

Module 4

Labelling

INNER LABELLING

1.3.1 Labelling

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ramipril / Hydrochlorothiazide Ranbaxy 2.5 mg / 12.5 mg Tablets
Ramipril / Hydrochlorothiazide Ranbaxy 5 mg / 25 mg Tablets

[To be completed nationally]

Ramipril/Hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH DATE

Lot

5. OTHER

-

OUTER LABELLING

1.3.1 Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ramipril / Hydrochlorothiazide Ranbaxy 2.5 mg / 12.5 mg Tablets
Ramipril / Hydrochlorothiazide Ranbaxy 5 mg / 25 mg Tablets

[To be completed nationally]

Ramipril/Hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains ramipril 2.5 mg and hydrochlorothiazide 12.5 mg.
Each tablet contains ramipril 5 mg and hydrochlorothiazide 25 mg.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet
[To be completed nationally]

14 Tablets
20 Tablets
28 Tablets
50 Tablets
100 Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Do not crush or chew.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25ºC.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION ON BRAILLE

Ramipril / Hydrochlorothiazide Ranbaxy 2.5 mg / 12.5 mg Tablets
Ramipril / Hydrochlorothiazide Ranbaxy 5 mg / 25 mg Tablets

[To be completed nationally]

Module 5

Scientific discussion during the initial procedure

I. Introduction

Based on the review of the data on quality, safety and efficacy, all the member states involved in the procedure considered that the applications for Ramipril/Hydrochlorothiazide Ranbaxy 2.5mg/12.5mg and 5mg/25 mg tablets (MA No 042745; Procedure No IT/H/0313/001-002/DC) could be approved. These products are prescription-only medicines indicated for the treatment of hypertension in patients whose blood pressure is not adequately controlled with ramipril alone or hydrochlorothiazide alone.

These applications were submitted using the Decentralised Procedure (DCP), with the Italy (IT) as Reference Member State (RMS) and Czech Republic, Germany, Spain and Poland as Concerned Member States (CMS). These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of TRIATEC HCT 2.5 mg/12.5 mg and 5 mg/25 mg, (Sanofi-Aventis S.p.A - Italy), registered since 15th November 1994.

Ramipril/Hydrochlorothiazide Ranbaxy tablets contain the active ingredients Ramipril and hydrochlorothiazide.
Ramipiril is an angiotensin-converting enzyme (ACE) inhibitor leading to decreased levels of angiotensin II (ANG II) and thus producing its therapeutic effects. Ramipril is prodrug of active angiotensin converting enzyme inhibitor, ramiprilat. Hydrochlorothiazide is a diuretic acting on the kidneys, mainly facilitating the Na^+ ion excretion, and thus producing its therapeutic effects.

It is recommended that Ramipril + Hydrochlorothiazide Ranbaxy is taken once daily, at the same time of the day, usually in the morning. Ramipril + Hydrochlorothiazide Ranbaxy 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.

One single-dose, bioequivalence study was submitted to support these applications, comparing the test product Ramipril/Hydrochlorothiazide 5 mg/25 mg tablets (Ranbaxy Laboratories Limited, India) with the reference product Delix® 5 plus tablets (Sanofi-Aventis Deutschland GmbH in Group), containing fixed dose combination of Ramipril 5 mg and Hydrochlorothiazide 25 mg. The study was conducted in healthy, adult, human subjects under fasting condition. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

II. About the product

Proposed name of the medicinal product in the RMS	Ramipril e Idroclorotiazide Ranbaxy
Name of the drug substances (INN name):	Ramipril and Hydrochlorotiazide
Pharmaco-therapeutic group (ATC Code):	Ramipril and diuretics, ATC code C09BA05
Pharmaceutical form(s) and strength(s):	Tablets 2,5 mg/ 12.5 mg, 5 mg/25mg
Reference Number(s) for the Decentralised Procedure	IT/H/0313/001-002/DC
Reference Member State:	IT
Concerned Member States:	CZ, DE, ES and PL
Marketing Authorisation Numbers	AIC No:042745012, 042745024 , 042745036, 042745048, 042745051, 042745063, 042745075, 042745087, 042745099, 042745101, 042745113, 042745125, 042745137, 042745149, 042745152, 042745164, 042745176, 042745188, 042745190, 042745202
Name and address of the Authorization Holder	Ranbaxy (UK) Limited Building 4, Chiswick Park, 566 Chiswick High Road, London, W45YE, United Kingdom

III. Scientific Overview and discussion

III.1 Quality aspects

ACTIVE SUBBSTANCE - RAMIPRIL

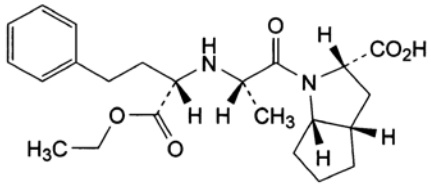
INN: Ramipril

Chemical Name: (2S,3aS,6aS)-1-[(S)-2-[[(S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]-octahydrocyclopenta[b]pyrrole-2-carboxylic acid.

Molecular Formula: $C_{23}H_{32}N_2O_5$

CAS number: 87333-19-5

Structure:



Molecular weight: 416.5 g/mol

Appearance: white or almost white, crystalline powder.

Solubility: sparingly soluble in water, freely soluble in methanol.

Ramipril is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance Ramipril, except for the proposed packaging specifications and stability data are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

ACTIVE SUBBSTANCE - HYDROCHLOROTHIAZIDE

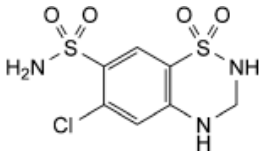
INN: Hydrochlorothiazide

Chemical Name: 6-chloro-3,4-dihydro-2H-1 ,2,4-benzothiadiazine-7-sulphonamide l ,1-dioxide;

Molecular Formula: $C_7H_8ClN_3O_4S_2$

CAS number: 58-93-5

Structure:



Molecular weight: 297.7 g/mol

Appearance: white or almost white, crystalline powder.

Solubility: very slightly soluble in water, soluble in acetone, sparingly soluble in ethanol (96%). It dissolves in dilute solutions of alkali hydroxides.

Hydrochlorothiazide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture, control and stability of the active substance hydrochlorothiazide are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other Ingredients

Other ingredients are: Hypromellose (Binder), Microcrystaline Cellulose (Diluent), Pregelatinised Starch (Disintegrant), Sodium Stearyl Fumarate (Lubricant). All the excipients comply with their respective European Pharmacopeia monographs. The qualitative formulation was developed and each of the excipients was selected for its intended use based on optimization studies. They are included in the formulation at suitable levels and for recognized purposes.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development

To seek essential similarity to the innovator product and to have a product similar in in-vivo performance to innovator product, strategy was to develop formulations of Ramipril and Hydrochlorothiazide 5/25 mg Tablets which is bioequivalent to the reference product of Delix® 5 Plus Tablets manufactured by Sanofi-Aventis S.p.A Strada Statale 17, KM 22 67019, Scoppito (L'Aquila), Italy.

Suitable pharmaceutical development data have been provided for these applications.

Comparative *in-vitro* dissolution and impurity profiles have been provided for these products and their respective reference products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of both strengths of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated.

Control of Finished Product

The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System

The tablets are packaged in Dessicant Embedded Cold form blister pack (OPA/Alu/PE/HDPE) & Triplex blister pack (PVC/PE/PVdC/Alu). These are packed into cardboard cartons with Patient Information Leaflets in a pack size of 14, 20, 28, 50 & 100 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuff.

Stability

Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results,

a shelf-life of 24 months has been proposed when the product is stored below 25º in the original package in order to protect from moisture.

III.2 Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of RAMIPRIL and HYDROCHLOROTIAZIDE in association are well known. RAMIPRIL and HYDROCHLOROTIAZIDE are well-known active substances and are widely used in combination. Thus based on the legislation requirements related to these kind of application ("generic application") no new additional studies are required for these applications related to Ramipril and Hydrochlorotiazide Ranbaxy.

III.3 Clinical aspects

The Clinical pharmacology of RAMIPRIL and HYDROCHLOROTIAZIDE is well-known. In accordance to the type of application ("generic application") data from a bioequivalence study (see detailes below) were provided. By legislation, no new pharmacodynamic or pharmacokinetic data are required for these applications related to Ramipril and Hydrochlorotiazide Ranbaxy.

Pharmacokinetics
In support of the application, the Marketing Authorisation Holder submitted the following bioequivalence study:

One single-dose, bioequivalence study, comparing the test product Ramipril/Hydrochlorothiazide 5 mg/25 mg tablets (Ranbaxy Laboratories Limited, India) with the reference product Delix® 5 plus tablets (Sanofi-Aventis Deutschland GmbH in Group), containing fixed dose combination of Ramipril 5 mg and Hydrochlorothiazide 25 mg. The study was conducted in healthy, adult, human subjects under fasting condition.

Acceptance criteria for assessing bioequivalence were satisfied for each pharmacokinetic parameter for both ramipril and hydrochlorothiazide. As for ramipril acceptance limits for C_{max} were widened to 77.65% – 128.79%, as the within subject variability of the reference product was 34.23%.

The results of the bioequivalence study with Ramipril 5 mg and Hydrochlorothiazide 25 mg formulation can be extrapolated to strength Ramipril 2.5 mg and Hydrochlorothiazide 12.5 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

EFFICACY
The efficacy of Ramipril and Hydrochlorothiazide is well-known. No new efficacy data have been submitted and none are required for applications of this type.

SAFETY
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues arose during the bioequivalence study.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN

The Applicant holds a Pharmacovigilance System Master File. All the documentation foreseen by the "Questions and Answers to support the implementation of the Pharmacovigilance legislation - UPDATE, NOVEMBER 2012" has been provided.

According to the "Module V- RMP" and the "Guidance on format of the RMP in the EU for Generics" RMP modules SI-SVII may be omitted for Generic Products. Thus, the final RMP submitted at the end of the procedure has been approved

SUMMARIES OF PRODUCT CHARACTERISTICS (Sm.PCs), PATIENT INFORMATION LEAFLETS (PILs) AND LABELLING

The SmPCs, PILs and labelling are acceptable from a clinical perspective. The SmPCs are consistent with those for the originator products. The PILs are consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with current guidance.

The packed leaflet has been evaluated via user consultatation study in accordance with the requirements of articles 59(3) and 61(1) of directive 2001/83/EC. The language used for the purpose of the user testing PIL was English.

IV Overall conclusions and benefit-risk assessment

This Application is related to the request of the Applicant Ranbaxy UK Limited for the Marketing Authorisation of a medicinal product containing Ramipril and Hydrochlorotiazide in tablet. The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of TRIATEC HCT 2.5 mg/12.5 mg and 5 mg/25 mg, (Sanofi-Aventis S.p.A - Italy), registered since 15th November 1994.

The quality characteristics Ramipril/Hydrochlorothiazide Ranbaxy 2.5 mg/12.5 mg and 5 mg/25 mg tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Based on the legislation requirements related to these kind of application ("generic application") data from a bioequivalence study were provided.

Bioequivalence has been demonstrated between the test product Ramipril/Hydrochlorothiazide 5 mg/25 mg tablets (Ranbaxy Laboratories Limited, India) and the reference product Delix® 5 plus tablets (Sanofi-Aventis Deutschland GmbH in Group), containing fixed dose combination of Ramipril 5 mg and Hydrochlorothiazide 25 mg. The results of the bioequivalence study with Ramipril 5 mg and Hydrochlorothiazide 25 mg formulation can be extrapolated to strength Ramipril 2.5 mg and Hydrochlorothiazide 12.5 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

No new non-clinical and clinical data were submitted in accordance to the legislation requirements, as the efficacy and safety profiles of Ramipril and Hydrochlorothiazide are well known. No new or unexpected safety concerns arose from the bioequivalence study.

The SmPCs, PILs and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along with current guidelines.

BENEFITI RISK ASSESSMENT

The quality of the products Ramipril/Hydrochlorothiazide Ranbaxy 2.5 mg/12.5 mg and 5 mg/25 mg tablets is acceptable, and no new non-clinical or clinical safety concerns have been identified.

Bioequivalence has been demonstrated between the test product Ramipril/Hydrochlorothiazide 5 mg/25 mg tablets (Ranbaxy Laboratories Limited, India) versus the reference product Delix® 5 plus tablets (Sanofi-Aventis Deutschland GmbH in Group), containing fixed dose combination of Ramipril 5 mg and Hydrochlorothiazide 25 mg. The results of the bioequivalence study with Ramipril 5 mg and Hydrochlorothiazide 25 mg formulation can be extrapolated to strength Ramipril 2.5 mg and Hydrochlorothiazide 12.5 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

Extensive clinical experience with Ramipril and Hydrochlorotiazide is considered to have demonstrated the therapeutic value of the products.

The benefit/risk balance is, therefore, considered to be positive.