ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTES OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Austria	SANOFI-AVENTIS GMBH OSTERREICH SATURN Tower Leonard-Bernstein-Straße 10 A-1220 Vienna Austria	Tritazide 25 mg/125 mg Tabletten Tritazide 5 mg/25 mg Tabletten	2,5 mg /12,5 mg 5 mg/25mg	Tablet	Oral
Austria	AstraZeneca Österreich GmbH Schwarzenbergplatz 7 A-1037 Wien Austria	HYPREN PLUS HYPREN PLUS FORTE	2.5 mg /12.5mg 5 mg/25mg	Tablets	Oral
Belgium	Sanofi-aventis Belgium Culliganlaan 1C 1831 Diegem Belgium	TRITAZIDE 5 mg – 25 mg, tabletten	5mg /25mg	Tablet	Oral
Bulgaria	AVENTIS PHARMA DEUTSCHLAND GMBH D-65926 Frankfurt am Main, Germany	TRITACE 2.5 PLUS	2.5 mg /12.5mg	Tablet	Oral
Bulgaria	SANOFI-AVENTIS BULGARIA EOOD Alexandar Stamboliyski blvd. 103 office building Sofia Tower, fl. 8, Sofia 1303 Bulgaria	TRITACE 2.5 PLUS TRITACE 5 PLUS	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral
Cyprus	SANOFI-AVENTIS CYPRUS LTD 14, Charalambou Mouskou street 2015 – Nicosia Cyprus	TRIATEC PLUS	5mg /25mg	Tablet	Oral
Czech Republic	sanofi-aventis, s.r.o. Evropská 2590/33c	TRITAZIDE 2.5/12.5mg TRITAZIDE 5/25mg	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	16000 Praha 6 Czech Republic				
Denmark	sanofi-aventis Denmark A/S Slotsmarken 13 2970 Hørsholm Denmark	TRIATEC COMP	5mg/25mg	Tablet	Oral
Estonia	SANOFI-AVENTIS DEUTSCHLAND GMBH 65926 Frankfurt am Main Germany	CARDACE COMP	2.5 mg /12.5mg	Tablet	Oral
Estonia	SANOFI-AVENTIS ESTONIA OÜ Pärnu mnt. 139 E/2 11317 Tallinn Estonia	CARDACE PLUS	5 mg/25mg	Tablet	Oral
Finland	SANOFI-AVENTIS OY Huopalahdentie 24 00350 Helsinki Finland	CARDACE COMP	2.5 mg /12.5mg	Tablet	Oral
France	SANOFI-AVENTIS France 1-13, boulevard Romain Rolland 75014 Paris France	COTRIATEC	5mg/12.5mg	Tablet	Oral
Germany	SANOFI-AVENTIS DEUTSCHLAND GMBH Brüningstraße 50 65926 Frankfurt am Main Germany	Delix 2,5 plus Delix 5 plus	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral
Germany	WINTHROP ARZNEIMITTEL GMBH Urmitzer Str. 5 56218 Mülheim-Kärlich Germany	Ramilich comp 2.5 mg /12.5 mg Taletten Ramilich comp 5 mg / 25 mg Tabletten	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral
Germany	WINTHROP ARZNEIMITTEL GMBH	RamiWin comp 2.5 mg/12.5 mg	2.5 mg /12.5mg	Tablet	Oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	Urmitzer Str. 5 56218 Mülheim-Kärlich Germany	Tabletten RamiWin comp 5 mg/25 mg Tabletten	5 mg/25mg		
Germany	AstraZeneca GmbH Tinsdaler Weg 183 22880 Wedel Germany	Vesdil 2.5 Plus Vesdil 5 Plus	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral
Greece	SANOFI-AVENTIS AEBE 348, Syggrou Avenue Building A 176-74 Kallithea Greece	TRIATEC PLUS TRIATEC PLUS	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral
Hungary	SANOFI-AVENTIS PRIVATE CO LTD H-1045 Budapest Tó u. 1.-5. Hungary	TRITACE HCT 2.5/12.5 Tabletta TRITACE HCT 5/25 Tabletta	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral
Hungary	Zentiva HU Kft Népfürdo u.22 1138 Budapest Hungary	RAMIPRIL HCT – ZENTIVA 2.5mg/12.5mg RAMIPRIL HCT – ZENTIVA 5mg/25mg	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral
Iceland	-				
Ireland	sanofi-aventis Ireland Ltd. Citywest Business Campus Dublin 24 Ireland	TRITAZIDE Tablets 2.5mg/12.5mg	2.5 mg /12.5mg	Tablet	Oral
Italy	SANOFI-AVENTIS SPA Viale Bodio, 37/b 20158 Milano Italy	TRIATEC HCT 2.5 TRIATEC HCT 5	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral
Italy	SANOFI-AVENTIS SPA Viale Bodio, 37/b 20158 Milano	RAMIPRIL E IDROCLORITIAZIDE SANOFI-AVENTIS	2.5 mg /12.5mg	Tablet	Oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	Italy	2.5mg/12.5mg RAMIPRIL E IDROCLORITIAZIDE SANOFI-AVENTIS 5mg/25mg	5 mg/25mg		
Italy	AstraZeneca S.p.A Palazzo Volta Via Francesco Sforza 20080 Basiglio (MI) Italy	UNIPRIL DIUR 2.5 mg + 12.5 mg compresse UNIPRILDIUR 5mg + 25 mg compresse	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral
Italy	POLIFARMA SPA Viale dell'Arte 69 00144 Roma Italy	IDROQUARK IDROQUARK	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral
Latvia	-				
Lithuania	-				
Luxembourg	Sanofi-aventis Belgium Culliganlaan 1C 1831 Diegem Belgium	TRITAZIDE	5mg /25mg	Tablet	Oral
Malta	-				
Netherlands	SANOFI-AVENTIS NETHERLANDS B.V. Kampenringweg 45 D-E (toren D en E) NL-2803 PE Gouda The Netherlands P.O. Box 2043 NL-2800 BD Gouda The Netherlands	TRITAZIDE Tabletten 5mg/25mg	5mg/25mg	Tablet	Oral
Norway	-				

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Poland	SANOFI-AVENTIS DEUTSCHLAND GMBH D-65926 Frankfurt am Main Germany	TRITACE 2.5 COMB TRITACE 5 COMB	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral
Portugal	Sanofi-Aventis Produtos Farmacêuticos, s.a. Empreendimento Lagoas Park, Edifício 7 - 3º Piso 2740-244 Porto Salvo Portugal	RAMICOR D 2.5 RAMICOR D 5	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral
Portugal	Sanofi-Aventis Produtos Farmacêuticos, s.a. Empreendimento Lagoas Park, Edifício 7 - 3º Piso 2740-244 Porto Salvo Portugal	TRIATEC COMPOSTO TRIATEC COMPOSTO FORTE	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral
Romania	AVENTIS PHARMA DEUTSCHLAND GMBH Brüningstraße 50 65926 Frankfurt am Main Germany	TRITACE 2.5 PLUS TRITACE 5 PLUS	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral
Slovak Republic	SANOFI-AVENTIS SLOVAKIA s.r.o., Žilinská 7-9 81105 Bratislava Slovak Republic	TRITAZIDE TRITAZIDE	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral
Slovenia	SANOFI-AVENTIS D.O.O. Dunajska cesta 119 1000 Ljubljana Slovenia	TRITAZIDE 2.5 5 mg/ 12,5 mg tablete TRITAZIDE 5 mg/ 25 mg tablete	2.5 mg /12.5mg 5 mg/25mg	Tablet	Oral
Spain	-				
Sweden	sanofi-aventis AB	TRIATEC COMP MITE	2.5 mg /12.5mg	Tablet	Oral

Member State EU/EEA	**Marketing Authorisation Holder**	**(Invented) name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
	Box 14142 167 14 Bromma Sweden	TRIATEC COMP	5 mg /25mg		
United Kingdom	-				

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF TRITAZIDE AND ASSOCIATED NAMES (SEE ANNEX I)

Tritazide contains Ramipril, a second-generation nonsulfhydryl angiotensin converting enzyme inhibitor (ACE-I), and Hydrochlorothiazide (HCTZ), a thiazide diuretic. Tritazide was included in the list of products for Summary of Products Characteristics (SPC) harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC, as amended, as the above-mentioned medicinal product does not have the same SPC across EU Member States, Iceland and Norway.

Critical Evaluation

A number of areas of disharmony in the product information for Tritazide have been evaluated by the CHMP and a revised PI was adopted. The main areas for harmonisation were as follows:

4.1 Therapeutic Indication

The combination is indicated for the treatment of hypertension in all Member States where licensed, although it is noted that terms including essential hypertension, arterial hypertension and arterial essential hypertension are used. The CHMP pointed out that this indication is limited to essential hypertension and the positioning of the indications is add-on therapy when each monotherapy has failed.

The combination 2.5mg /12.5mg led to greater reduction in blood pressure than the treatment with individual components, and the combination of 5mg/25mg produced a better therapeutic effect than doubling the ramipril dose to 10mg.

Considering that no major concern can be established concerning the safety, efficacy and clinical adverse event of the ramipril/HCTZ combination in non responders to HCTZ and ramipril alone, the CHMP adopted the following two harmonised wordings for indications:

-Treatment of essential 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

In most cases the initial dose is the same, but there are differences with respect to subsequent titration (both in terms of frequency of increase and maximum daily dose).

Considering a paucity of trial data assessing titration steps with the combination the posology has been amended. The CHMP adopted the harmonised wording:

"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.

TRITAZIDE and associated names 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"

4.3 Contra-indications

The majority of the contraindications are related to use of ramipril as a component of the Tritazide. They are extended with the contraindications of HCTZ. There were however some contraindications with HCTZ labelled in some local SPC's and not proposed in the harmonised SPC. There were other contraindications in local SPC-s like acute hypertension or primary aldosteronism but they are not contraindications but rather non-indication in Europe.

The CHMP adopted the harmonised wording for the contra-indictations:

-Hypersensitivity to the active substance or to any other ACE (Angiotensin Converting Enzyme) inhibitor, hydrochlorothiazide, other thiazide diuretics, sulphonamides or any of the excipients of TRITAZIDE and associated names (see section 6.1).
- History of hereditary or idiopathic angioedema
- 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 section 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 TRITAZIDE (see section 4.4)
- Severe impairment of liver function, hepatic encephalopathy

4.4 Special warnings and precautions for use

The CHMP included under this session the warning about Primary Hyperaldosteronism, therefore adopted the following harmonised wording: "*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"*.
The CHMP also noted the importance to insert a paragraph regarding cough in line with the warning of previously harmonised ACE-I, therefore agreed the following:
"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"

The CHMP also adopted a harmonised wording regarding pregnancy and lactation under this section (see SPC).

4.5 Interaction

The list of products which interact or may interact with Tritazide is acceptable. The CHMP adopted the proposed interactions under this section.

4.6 Pregnancy and lactation

The CHMP recommended a contraindication only for the second and third trimester of pregnancy in line with PhVWP wording on use of AEC-I in pregnancy. However the company challenged this view and proposed a contraindication through out pregnancy, based on data from the ramipril pregnancy register.
The text agreed in the PhVWP of this warning doesn't encourage or propose the use of ACE inhibitors during the first trimester of the pregnancy on the contrary once the pregnancy is detected the prescriber has to stop the use of ACE inhibitors and to change if it is necessary for another anti-hypertensive agent as soon as possible. This change of the text is to ensure it doesn't suggest an immediate artificial abortion, which is not justified by the clinical experiences collected till now.
In conclusions, the CHMP adopted a harmonised wording in line with PhVWP wording on use of AEC-I in pregnancy. In conclusion, the CHMP adopted a harmonised wording according to the PhVWP recommendations: "*Tritazide 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. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also section 4.3 and 4.4)".

GROUNDS FOR AMENDMENT OF THE SUMMARYOF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics, labelling and package leaflet.

- the Summaries of Products Characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CHMP has recommended the amendment of the Marketing Authorisation(s) for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Tritazide and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

1. NAME OF THE MEDICINAL PRODUCT

TRITAZIDE and associated names (see Annex I) 2.5 mg/12.5 mg tablets
TRITAZIDE and associated names (see Annex I) 5 mg/12.5 mg tablets
TRITAZIDE and associated names (see Annex I) 5 mg/25 mg tablets

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
[To be completed nationally]

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 TRITAZIDE is taken once daily, at the same time of the day, usually in the morning.

TRITAZIDE can be taken before, with or after meals, because food intake does not modify its bioavailability (see section 5.2).
TRITAZIDE has to be swallowed with liquid. It must not be chewed or crushed.

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.

TRITAZIDE 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 TRITAZIDE.

Patients with renal impairment
TRITAZIDE 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 TRITAZIDE. 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 TRITAZIDE 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.
TRITAZIDE 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
TRITAZIDE 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 TRITAZIDE (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 TRITAZIDE (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 TRITAZIDE. 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 TRITAZIDE 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 TRITAZIDE (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 TRITAZIDE 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 TRITAZIDE 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.

4.6 Pregnancy and lactation

TRITAZIDE 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.

TRITAZIDE 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 including blurred vision, conjunctivitis		Xanthopsia, 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 system and breast disorders		Transient erectile impotence		Libido decreased, gynaecomastia
Psychiatric disorders		Depressed mood, apathy, anxiety, nervousness, sleep disorders including somnolence,		Confusional state, restlessness, disturbance in attention

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 %.

Metabolism
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 %.

Metabolism
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

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]
{Name and address}
{tel}
{fax}
{e-mail}

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]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

TRITAZIDE and associated names (see Annex I) 2.5 mg/12.5 mg tablets
TRITAZIDE and associated names (see Annex I) 5 mg/12.5 mg tablets
TRITAZIDE and associated names (see Annex I) 5 mg/25 mg tablets

[See Annex I - to be completed nationally]

ramipril/hydrochlorothiazide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

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

[See Annex I - To be completed nationally

{Name and address}
{Tel}
{fax}
{e-mail}

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

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

TRITAZIDE and associated names (see Annex I) 2.5 mg/12.5 mg tablets
TRITAZIDE and associated names (see Annex I) 5 mg/12.5 mg tablets
TRITAZIDE and associated names (see Annex I) 5 mg/25 mg tablets

[See Annex I - to be completed nationally]

ramipril/hydrochlorothiazide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - to be completed nationally]

{Name}

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

TRITAZIDE and associated names (see Annex I) 2.5 mg/12.5 mg tablets
TRITAZIDE and associated names (see Annex I) 5 mg/12.5 mg tablets
TRITAZIDE and associated names (see Annex I) 5 mg/25 mg tablets
[See Annex I - To be completed nationally]

Ramipril/Hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine.
- 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. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet

1. WHAT TRITAZIDE IS AND WHAT IT IS USED FOR

TRITAZIDE 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.

TRITAZIDE 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. BEFORE YOU TAKE TRITAZIDE

Do not take TRITAZIDE:
- If you are allergic (hypersensitive) to ramipril, hydrochlorothiazide or any of the other ingredients of TRITAZIDE (see section 6)
- If you are allergic (hypersensitive) to medicines similar to TRITAZIDE (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, TRITAZIDE 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 TRITAZIDE if any of the above apply to you. If you are not sure, talk to your doctor before taking TRITAZIDE**.**

Take special care with TRITAZIDE
Check with your doctor or pharmacist before taking your medicine:
- 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 TRITAZIDE 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. TRITAZIDE 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
TRITAZIDE 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 any of the above apply to you (or you are not sure), talk to your doctor before taking TRITAZIDE.

Taking TRITAZIDE with other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription (including herbal medicines). This is because TRITAZIDE can affect the way some other medicines work. Also some medicines can affect the way TRITAZIDE works.

Please tell your doctor if you are taking any of the following medicines. They can make TRITAZIDE 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 TRITAZIDE:
- 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 TRITAZIDE:
- Medicines for diabetes such as oral glucose lowering medicines and insulin. TRITAZIDE may lower your blood sugar amounts. Check your blood sugar amounts closely while taking TRITAZIDE
- Lithium (for mental health problems). TRITAZIDE 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 TRITAZIDE.

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

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

Pregnancy and breast-feeding
You must tell your doctor if you think that you are (or might become) pregnant
You should not take TRITAZIDE 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 TRITAZIDE, 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 TRITAZIDE 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 TRITAZIDE. This is more likely to happen when you start taking TRITAZIDE or start taking a higher dose. If this happens, do not drive or use any tools or machines.

3. HOW TO TAKE TRITAZIDE

Always take TRITAZIDE exactly as your doctor has told you. You should 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.

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 TRITAZIDE 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 TRITAZIDE
- 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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

Stop taking TRITAZIDE 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 TRITAZIDE
- 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 TRITAZIDE 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 notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TRITAZIDE

[To be completed nationally]

6. FURTHER INFORMATION

What TRITAZIDE contains

[To be completed nationally]

What TRITAZIDE looks like and contents of the pack

Tablets
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

{Name and address}
{tel}
{fax}
{email}

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

Austria:
Tritazide 2.5 mg/12.5 mg Tabletten, Tritazide 5 mg/25 mg Tabletten
Hypren Plus 2.5 mg/12.5 mg Tabletten, Hypren Plus Forte 5 mg/25 mg Tabletten

Belgium:
Tritazide 5 mg/25 mg tabletten/comprimés/Tabletten

Bulgaria:
Tritace 2.5 Plus 2.5 mg/12.5 mg таблетки, Tritace 5 Plus 5 mg/25 mg таблетки

Cyprus:
Triatec Plus 5 mg/25 mg δισκία

Czech Republic
Tritazide 2.5 mg/12.5 mg tablety, Tritazide 5 mg/25 mg tablety

Denmark:
Triatec Comp 5 mg/25 mg tabletter

Estonia:
Cardace Comp 2.5 mg/12.5 mg tabletid
Cardace Plus 5 mg/25 mg tabletid

Finland:
Cardace Comp 2.5 mg/12.5 mg tabletit

France:
Cotriatec 5 mg/25 mg comprimés

Germany:
Delix 2.5 Plus 2.5 mg/12.5 mg Tabletten, Delix 5 Plus 5 mg/25 mg Tabletten
Ramilich Comp 2.5 mg/12.5 mg Tabletten, Ramilich Comp 5 mg/25 mg Tabletten
Vesdil 2.5 Plus 2.5 mg/12.5 mg Tabletten, Vesdil 5 Plus 5 mg/25 mg Tabletten

Greece:
Triatec Plus 2.5 mg/12.5 mg δισκία, Triatec Plus 5 mg/25 mg δισκία

Hungary:
Tritace HCT 2.5 mg/12.5 mg tabletta, Tritace HCT 5 mg/25 mg tabletta
Ramiwin HCT 2.5 mg/12.5 mg tabletta, Ramiwin HCT 5 mg/25 mg tabletta

Ireland:
Tritazide tablets 2.5 mg/12.5 g

Italy:
Triatec HCT 2.5 mg/12.5 mg compresse, Triatec HCT 5 mg/25 mg compresse
Ramipril E Idrocloritiazide sanofi-aventis 2.5 mg/12.5 mg compresse
Ramipril E Idrocloritiazide sanofi-aventis 5 mg/25 mg compresse
Unipril Diur 2.5 mg/12.5 mg compresse, Unipril Diur 5 mg/25 mg compresse
Idroquark 2.5 mg/12.5 mg compresse, Idroquark 5 mg/25 mg compresse

Luxembourg:
Tritazide 5/25 mg tabletten/comprimés/Tabletten

Netherlands:
Tritazide 5 mg/25 mg tabletten

Poland:
Tritace 2.5 Comb 2.5 mg/12.5 mg tabletki, Tritace 5 Comb 5 mg/25 mg tabletki

Portugal:
Ramicor D 2.5 mg/12.5 mg comprimidos, Ramicor D 5 mg/25 mg comprimidos
Triatec Composto 2.5 mg/12.5 mg comprimidos, Triatec Composto Forte 5 mg/25 mg comprimidos

Romania:
Tritace 2.5 Plus 2.5 mg/12.5 mg comprimate, Tritace 5 Plus 5 mg/25 mg comprimate

Slovak Republic:
Tritazide 2.5 mg/12.5 mg tablety, Tritazide 5 mg/25 mg tablety

Slovenia:
Tritazide 2.5 mg/12.5 mg tablete, Tritazide 5 mg/25 mg tablete

Sweden:
Triatec Comp Mite 2.5 mg/12.5 mg tabletter, Triatec Comp 5 mg/25 mg tabletter

This leaflet was last approved in: {MM/YYYY}
[To be completed nationally]

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.