Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tritace 2.5 mg Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg ramipril.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Product as imported from the Netherlands and Poland:
Yellow, oblong tablets marked with ‘2.5’ and ‘HMR’ on either side of a scoreline on one side and ‘2.5’and the Aventis logo on either side of a scoreline on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tritace is indicated in the treatment of all grades of hypertension.

Congestive heart failure; as adjunctive therapy to diuretics with or without cardiac glycosides.

Tritace has been shown to reduce mortality when administered to patients surviving acute myocardial infarction with clinical evidence of heart failure.

Non-diabetic and diabetic overt nephropathy

Treatment of overt glomerular nephropathy. Ramipril decreases the rate of progression of renal insufficiency and of the development of end-stage renal failure (needs for dialysis or renal transplantation)

Non-diabetic and diabetic incipient nephropathy

Treatment of incipient nephropathy. Ramipril reduces the albumin excretion rate.

Prevention of myocardial infarction, stroke or cardiovascular death in patients with an increased cardiovascular risk who are already taking standard therapy.

Prevention of myocardial infarction, stroke or cardiovascular death in type 2 diabetic patients with an increased cardiovascular risk.

Prevention of progression of microalbuminuria to overt nephropathy.

4.2 Posology and method of administration

Oral Administration.

Tritace Tablets should be taken with plenty of liquid. The absorption of ramipril is not affected by food. The tablets must not be chewed.

Hypertension:
The recommended initial dosage in patients not on diuretics and without congestive heart failure is 2.5 mg Tritace once a day. Dosage should be increased incrementally at intervals of 1-2 weeks, based on patient response, up to a maximum of 10 mg once a day.

A 1.25 mg dose will only achieve a therapeutic response in a minority of patients. The usual maintenance dose range is 2.5-5 mg Tritace as a single daily dose. If the patient response is still unsatisfactory at the maximum dose of 10 mg Tritace, combination treatment is recommended.

Diuretic-treated patients,
The diuretic should be discontinued 2-3 days before beginning therapy with Tritace to reduce the likelihood of symptomatic hypotension. It may be resumed later if required. If the diuretic therapy cannot be discontinued, the initial dose of Tritace should be 1.25 mg.

Congestive heart failure:
Recommended initial dose: In patients stabilised on diuretic therapy the initial dose is 1.25 mg once daily. Depending on the patient's response, the dose may be increased. It is recommended that the dose, if increased, be doubled at intervals of 1 to 2 weeks. If a daily dose of 2.5 mg or more is required, this may be taken as a single dose or as two divided doses. Maximum permitted daily dose: 10 mg.

In order to minimise the possibility of symptomatic hypotension, patients on previous high dose diuretics should have the diuretic dose reduced before starting Tritace.

Post myocardial infarction:
Initiation of therapy: treatment must be started in hospital between day 3 and day 10 following AMI. The starting dose is 2.5 mg twice a day which is increased to 5 mg twice a day after 2 days. If the initial 2.5 mg dose is not tolerated a dose of 1.25 mg twice a day should be given for two days before increasing to 2.5 mg and 5.0 mg twice a day. If the dose cannot be increased to 2.5 mg twice a day treatment should be withdrawn. Maintenance dose: 2.5 to 5.0 mg twice a day.

Dosage adjustment in renal impairment
The usual dose of Tritace is recommended for patients with a creatinine clearance>30 ml/min (serum creatinine <165 mol/l). For patients with a creatinine clearance <30 ml/min (serum creatinine>165 mol/l) the initial dose is 1.25 mg Tritace once daily and the maximum dose 5 mg Tritace once daily.

In patients with severe renal impairment (creatinine clearance <10 ml/min and serum creatinine of 400-650 mol/l), the recommended initial dose is also 1.25 mg Tritace once a day, but the maintenance dosage should not exceed 2.5 mg Tritace once a day.

Dosage in hepatic impairment:
In patients with impaired liver function the metabolism of the parent compound ramipril, and therefore the formation of the bioactive metabolite ramiprilat, is reduced due to diminished activity of esterases in the liver, resulting in elevated plasma ramipril levels. Treatment with Tritace should therefore be initiated at a reduced dose under close medical supervision in patients with impaired liver function.

Elderly:
There are no special dosage recommendations for elderly patients, apart from the general warning about patients with renal or hepatic insufficiency or congestive heart failure which may be more common in older patients, and concomitant use of diuretic drugs. The dose should be titrated according to need for the control of blood pressure.

Children:
Tritace has not been studied in children, and therefore use in this age group is not recommended.

Cardiac failure
In hypertensive patients who also have congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients therapy should be started at a dose of 1.25mg under close medical supervision in hospital.

Non-Diabetic & Diabetic Overt &Incipient Nephropathy
Recommended initial dose: 1.25mg Tritace once daily. Depending on how the patient tolerates the drug, the dose should be increased. It is recommended that the dose, if increased, be doubled at intervals of 2 to 3 weeks. Maximum permitted daily dose: 5mg Tritace.

In patients pretreated with a diuretic, consideration must be given to discontinuing the diuretic at least 2 to 3 days or – depending on the duration of action of the diuretic -longer before starting treatment with Tritace, or at least to reducing the diuretic dose.

In patients with impaired liver function, the response to treatment with Tritace may be either increased or reduced. Treatment in these patients must therefore be initiated only under close medical supervision. The maximum permitted daily dose in such cases is 2.5mg Tritace.

Prevention of myocardial infarction, stroke or cardiovascular death in patients with an increased cardiovascular risk who are already taking standard therapy;
The recommended initial dose is 2.5 mg Tritace once daily. Depending on the tolerability, the dose is gradually increased. It is recommended to double the dose after one week of treatment and after another three weeks to increase it to 10 mg. The usual maintenance dose is 10 mg Tritace daily.

Prevention of myocardial infarction, stroke or cardiovascular death in type 2 diabetic patients with an increased cardiovascular risk.
The recommended initial dose is 2.5 mg Tritace once daily. Depending on the tolerability, the dose is gradually increased. It is recommended to double the dose after one week of treatment and after another three weeks to increase it to 10 mg. The usual maintenance dose is 10 mg Tritace daily.

Prevention of progression of microalbuminuria to overt nephropathy:
The recommended initial dose is 2.5 mg Tritace once daily. Depending on the tolerability, the dose is gradually increased. It is recommended to double the dose after one week of treatment and after another three weeks to increase it to 10 mg. The usual maintenance dose is 10 mg Tritace daily.

4.3 Contraindications

- Hypersensitivity to ramipril or excipients.
- Use in patients with a history of angioneurotic oedema relating to previous treatment with an ACE inhibitor.
- Pregnancy and lactation.
- Use in children.

4.4 Special warnings and precautions for use

Tritace should not be used in patients with aortic stenosis or outflow obstruction.

Assessment of renal function: Evaluation of the patient should include assessment of renal function prior to initiation of therapy and during treatment.

Impaired renal function: Patients with renal insufficiency may require reduced or less frequent doses of Tritace; their renal function should be closely monitored. In themajority, renal function will not alter.

There is a risk of impairment of renal function, particularly in patients with renal insufficiency, congestive heart failure, bilateral renal artery stenosis and unilateral renal artery stenosis in the single kidney as well as after renal transplantation.

This may be related to the functional role of angiotensin II in maintaining glomerular filtration pressure. It may not be possible to achieve a maximal response in blood pressure and maintain adequate renal perfusion. If recognised early, such impairment of renal function is reversible upon discontinuation of therapy.

Patients haemodialysed using high-flux polyacrylonitrile ('AN69') membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes for dialysis.

Similar reactions have been observed during low-density lipoprotein apheresis with dextran sulphate. This method should, therefore, not be used in patients treated with ACE inhibitors.

Some hypertensive patients with no apparent pre-existing renal disease, may develop minor and usually transient increases in blood urea nitrogen and serum creatinine when Tritace is given, in particular concomitantly with a diuretic. Dosage reduction of Tritace and/or discontinuation of the diuretic may be required. Additionally, in patients with renal insufficiency, there is a risk of hyperkalaemia.

Impaired liver function: As ramipril is a prodrug metabolised to its active moiety in the liver, particular caution and close monitoring should be applied to patients with impaired liver function. The metabolism of the parent compound, and therefore the formation of the bioactive metabolite ramiprilat, may be diminished resulting in markedly elevated plasma levels of the parent compound (due to the reduced activity of esterases in the liver).

Malignant hypertension: In patients with severe malignant hypertension, treatment with Tritace should be initiated in hospital under close supervision.

Symptomatic hypotension: In patients with uncomplicated hypertension, symptomatic hypotension has been observed rarely after the initial dose of Tritace as well as after increasing the dose of Tritace. It is more likely to occur in patients who have been volume- and salt-depleted by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, vomiting or in patients with severe heart failure. Therefore, in these patients, diuretic therapy should be discontinued and volume and/or salt depletion should be corrected before initiating therapy with Tritace.

If symptomatic hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of physiological saline. Intravenous atropine may be necessary if there is associated bradycardia. Treatment with Tritace may usually be continued following restoration of effective blood volume and blood pressure.

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria or azotemia. In these patients, therapy should be started under close medical supervision.

Surgery/anaesthesia: In patients undergoing surgery or during anaesthesia with agents producing hypotension, Tritace may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Agranulocytosis and bone marrow depression: In patients on angiotensin converting enzyme inhibitors, agranulocytosis and bone marrow depression have been seen rarely, as well as a reduction in red cell count, haemoglobin content and platelet count. These are more frequent in patients with renal impairment, especially if they also have a collagen vascular disease. Regular monitoring of white blood cell counts and protein levels in urine should be considered in patients with collagen vascular disease (e.g. lupus erythematosus and scleroderma), especially associated with impaired renal function and concomitant therapy particularly with corticosteroids and antimetabolites. Patients on allopurinol, immunosuppressants and other substances that may change the blood picture also have increased likelihood of other blood picture changes.

Hyperkalaemia: Elevated serum potassium has been observed very rarely in hypertensive patients. Risk factors for the development of hyperkalaemia include renal insufficiency, potassium sparing diuretics and the concomitant use of agents to treat hypokalaemia.

Angioneurotic oedema: Angioneurotic oedema has been reported rarely with ACE inhibitors including Tritace. In some cases, symptoms have been observed up to 2 years after initiation of treatment. Such reactions should be regarded as an indication to discontinue therapy immediately and the patient closely monitored.

Where swelling is confined to the face, lips and mouth, the condition will usually resolve without further treatment, although antihistamine may be useful in relieving symptoms. These patients should be followed carefully until the swelling has resolved.

However, where there is involvement of the tongue, glottis and/or larynx, likely to cause airways obstruction, appropriate therapy such as subcutaneous adrenaline (0.5 mil 1:1000) should be administered promptly when indicated.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor *(see also 'Contraindications').* Other hypersensitivity reactions have been reported.

4.5 Interaction with other medicinal products and other forms of interaction

Combination with diuretics or other antihypertensive agents (e.g. β-adrenoceptor blockers, methyldopa), may potentiate the antihypertensive response to Tritace. Ganglionic and adrenergic blocking drugs should only be combined with ramipril under careful supervision. Concomitant propranolol may reduce the bioavailability of ramipril, but this does not appear to be clinically significant. There is no experience of the use of ramipril with calcium antagonists.

Potassium sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements may increase the risk of hyperkalaemia. Tritace may attenuate the potassium loss caused by thiazide-type diuretics. If concomitant use of these agents is indicated, they should be given with caution and serum potassium should be monitored regularly.

When antidiabetic agents (insulin and sulphonylurea derivatives) are used concurrently, the possibility of increased blood-sugar reduction must be considered.

When ACE inhibitors are administered simultaneously with non-steroidal anti- inflammatory drugs (e.g. acetylsalicylic acid and indomethacin), attenuation of the antihypertensive effect may occur.

If Tritace is given with lithium, an increase in serum lithium concentration may occur.

4.6 Pregnancy and lactation

Tritace is contra-indicated during pregnancy and lactation. Pregnancy should be excluded before start of treatment with Tritace and avoided during treatment; exposure of the mother to ACE inhibitors in mid or late pregnancy has been associated with oligohydramnios and neonatal hypotension with anuria or renal failure.

From animal experiments it is known that use of ramipril may cause a decreased utero-placental perfusion. There is also a potential risk of foetal or post-natal effect as ACE inhibitors also influence the local renin-angiotensin system. In peri- post natal studies increased renal pelvic dilatation was observed in the first generation offspring. However, ramipril was not fetotoxic in our studies although ACE inhibitors have shown fetotoxicity in some species.

Tritace should not be used during lactation.

4.7 Effects on ability to drive and use machines

In individual cases, as a result of a reduction in blood pressure, treatment with Tritace may affect the ability to drive and operate machinery. This occurs especially at the start of treatment, when changing over from other preparations and during concomitant use of alcohol. 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

Generally, adverse reactions are mild and transient, and do not require discontinuation of therapy. The most frequently reported adverse reactions are nausea, dizziness and headache.

Cardiovascular: Symptomatic hypotension accompanied by dizziness, weakness and nausea may occur after the initial dose of Tritace and after an increase in the dose of Tritace. It has been rarely observed, but may occur in severely salt/volume-depleted patients such as those treated with diuretics, patients on dialysis and in patients with severe congestive heart failure. Syncope has also been observed rarely.

Myocardial infarction or cerebrovascular accident possibly secondary to severe hypotension in high risk patients, chest pain, palpitations, rhythm disturbances, angina pectoris may occur.

Renal: Treatment with Tritace may impair renal function.

*Gastrointestinal:*Treatment with Tritace may be associated with symptoms in the digestive tract, e.g. dryness of the mouth, irritation or inflammation of the oral mucosa, digestive disturbances, constipation, diarrhoea, nausea and vomiting, (gastritis-like) stomach pain, upper abdominal discomfort (sometimes with increased levels of pancreatic enzymes), increases in hepatic enzymes and/or serum bilirubin, jaundice due to impaired excretion of bile pigment (cholestatic jaundice), other forms of impaired liver function, and hepatitis.

Pancreatitis has been reported rarely in patients treated with ACE inhibitors; in some cases this has proved fatal.

Allergic: Hypersensitivity reactions accompanied by pruritus, rash, shortness of breath and sometimes fever may occur, but usually resolve spontaneously after withdrawal of Tritace.

In addition, the following cutaneous and mucosal reactions may occur: reddening of skin areas with accompanying heat sensation, conjunctivitis, itching, urticaria, other skin or mucosal eruptions (maculo-papular and lichenoid exanthema and enanthema), sometimes pronounced hair loss, and precipitation or intensification of Raynaud's phenomenon. Other skin and mucosal reactions (erythema multiforme, psoriasiform and pemphigoid exanthema and enanthema), hypersensitivity of the skin to light, and loosening of the nails (onycholysis) have been observed with ACE inhibitors.

Vasculitis, muscle and joint pains, fever or eosinophilia may occur. Raised titres of antinuclear antibodies have been seen with other ACE inhibitors.

Angioneurotic oedema: In very rare cases angioneurotic oedema has occurred during therapy with ACE inhibitors including Tritace. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment with Tritace must be discontinued and appropriate therapy instituted immediately.

Respiratory tract: A dry tickling cough occurs frequently. This is possibly due to the desired ACE inhibition as are the following adverse effects: rhinitis, sinusitis, bronchitis and, especially in patients with tickling cough, bronchospasm.

Other adverse reactions: Disturbances of balance, headache, nervousness, restlessness, tremor, sleep disorders, confusion, loss of appetite, depressed mood, feeling of anxiety, paraesthesiae, taste change, taste reduction and sometimes loss of taste, muscle cramps, erectile impotence and reduced sexual desire may occur.

Laboratory test findings: Increases in blood urea nitrogen and serum creatinine may occur, in particular with renal insufficiency or in patients pretreated with a diuretic. Pre-existing proteinuria may deteriorate.

Serum sodium levels may decrease. Elevation of serum potassium may occur, since Tritace leads to a decrease in aldosterone secretion; potassium sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements should therefore be avoided.

Slight decrease in haemoglobin, haematocrit and white cell count as well as elevation of liver enzymes, have been reported in a few patients, but a causal relationship to ramipril has not been established.

4.9 Overdose

In case of overdosage prolonged hypotension is to be expected. Treatment with an intravenous infusion of physiological saline and/or angiotensin II may be required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ramipril is a prodrug which, after absorption from the gastrointestinal tract, is hydrolysed in the liver to form the active angiotensin converting enzyme (ACE) inhibitor, ramiprilat which is a potent and long acting ACE inhibitor. Administration of ramipril causes an increase in plasma renin activity and a decrease in plasma concentrations of angiotensin II and aldosterone. The beneficial haemodynamic effects resulting from ACE inhibition are a consequence of the reduction in angiotensin II causing dilatation of peripheral vessels and reduction in vascular resistance. There is evidence suggesting that tissue ACE particularly in the vasculature, rather than circulating ACE, is the primary factor determining the haemodynamic effects.

Angiotensin converting enzyme is identical with kininase II, one of the enzymes responsible for the degradation of bradykinin. There is evidence that ACE inhibition by ramiprilat appears to have some effects on the kallikrein-kinin-prostaglandin systems. It is assumed that effects on these systems contribute to the hypotensive and metabolic activity of ramipril.

Administration of Tritace to hypertensive patients results in reduction of both supine and standing blood pressure. The antihypertensive effect is evident within one to two hours after the drug intake; peak effect occurs 3-6 hours after drug intake and has been shown to be maintained for at least 24 hours after usual therapeutic doses.

Ramipril is rapidly absorbed and hydrolysed to ramiprilat a highly specific, long acting, non-sulphydryl angiotensin converting enzyme inhibitor. Its onset of action begins gradually within one hour and its effects continue usually for 24 hours after a single daily dose.

Data indicate no loss of effect during long term therapy. Rebound hypertension does not occur following abrupt cessation of therapy. In patients with non-diabetic or diabetic overt nephropathy, ramipril decreases the rate of progression of renal insufficiency and the development of end stage renal failure and therewith the need for dialysis or renal transplantation. In patients with non diabetic incipient nephropathy, ramipril reduces the albumin excretion rate.

Revascularisation procedures were performed in patients with an increased cardiovascular risk such as manifest coronary heart disease (with or without a history of myocardial infarction), a history of stroke, or a history of peripheral vascular disease. Revascularisation parameters showed a reduction in events versus placebo however the number of patients, particularly in non-cardiovascular interventions was small.

In patients with diabetes in association with at least one additional risk factor (microalbuminuria, hypertension, high cholesterol, low HDL cholesterol, or current smoking), ramipril reduces the rate of diabetic complications (overt nephropathy, or the need for dialysis).

5.2 Pharmacokinetic properties

Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract, peak plasma concentrations of ramipril are reached within one hour. Peak plasma concentrations of the active metabolite, ramiprilat, are reached within 2-4 hours.

Plasma concentrations of ramiprilat decline in a polyphasic manner. The effective half-life of ramiprilat after multiple once daily administration of ramipril is 13--17 hours for 5--10 mg ramipril and markedly longer for lower doses, 1.25-2.5 mg ramipril. This difference is related to the long terminal phase of the ramiprilat concentration time curve observed at very low plasma concentrations. This terminal phase is independent of the dose, indicating a saturable capacity of the enzyme to bind ramiprilat. 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.

Ramipril is almost completely metabolised and the metabolites are excreted mainly via the kidneys. In addition to the bioactive metabolite, ramiprilat, other, inactive metabolites have been identified, including diketopiperazine ester, diketopiperazine acid and conjugates.

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

5.3 Preclinical safety data

Reproduction toxicology studies in the rat, rabbit and monkey did not disclose any teratogenic properties. Fertility was not impaired either in male or in female rats. The administration of ramipril to female rats during the fetal period and lactation produced irreversible renal damage (dilatation of the renal pelvis) in the offspring at daily doses of 50 mg/kg body weight and higher.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Pregelatinised maize starch
Microcrystalline cellulose
Sodium stearyl fumarate
Yellow Ferric oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

- Store in the original package.
- Do not store above 25ºC

6.5 Nature and contents of container

Blister packs of 28 or 30 tablets contained in an outer cardboard carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Tritace tablets should be taken with plenty of liquid
The absorption of ramipril is not affected by food.
Tablets must not be chewed.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing Limited
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 0465/163/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 July 2005

10 DATE OF REVISION OF THE TEXT

August 2009