IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0540/084/003
Case No: 2060254

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

sanofi-aventis Ireland Limited

Citywest Business Campus, **Dublin 24**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Tritace 5mg Capsules

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **03/02/2009** until **07/03/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tritace 5 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 5.0 mg ramipril.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Gelatin capsule, hard.
Scarlet opaque/white opaque gelatin capsule, containing a white powder mixture.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tritace is indicated in the treatment of all grades 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 capsules should be taken with plenty of liquid. The absorption of ramipril is not affected by food.

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

A 1.25mg dose will only achieve a therapeutic response in a minority of patients. The usual effective dose range is 2.5 - 10mg Tritace as a single daily dose. If the patient response is still unsatisfactory at the maximum dose of 10mg 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. If the diuretic cannot be discontinued, the initial dose of Tritace should be 1.25mg.

Dosage adjustment in renal impairment:
With a creatinine clearance between 50 and 20ml/min per 1.73m^2 body surface area, the initial daily dose is generally 1.25mg Tritace. The maximum permitted daily dose in this case is 5mg Tritace.

Warning: Insufficient experience has been gained concerning the use of Tritace in children and in dialysis patients.

Patients with incompletely corrected fluid or salt depletion, in patients with severe hypertension, as well as in patients in whom a hypotensive reaction would constitute a particular risk (e.g. with relevant stenoses of the coronary vessels or those supplying the brain): A reduced initial dose of 1.25mg of Tritace daily must be considered.

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 a diminished activity of esterases in the liver, resulting in elevated plasma ramipril levels. Treatment with Tritace should therefore be initiated with a reduced dose under close medical supervision in patients with impaired hepatic function. The maximum permitted daily dose in such cases is 2.5mg Tritace.

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. A reduced initial dose of 1.25mg Tritace daily must be considered.

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

Congestive heart failure: Recommended initial dose: In patients stabilised on diuretic therapy the initial dose is 1.25mg 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 2.5mg or more is required, this may be taken as a single dose or as two divided doses. Maximum permitted daily dose: 10mg

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 2.5mg twice a day which is increased to 5mg twice a day after 2 days. If the initial 2.5mg dose is not tolerated, a dose of 1.25mg twice a day should be given for two days before increasing to 2.5mg and 5.0mg twice a day. If the dose cannot be increased to 2.5mg twice a day, treatment should be withdrawn. Maintenance dose: 2.5 to 5.0mg twice a day. Maximum permitted daily dose: 10mg Tritace.

Special Groups

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 pre-treated 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

Tritace should not be used:
- in patients with hypersensitivity to ramipril, to any other ACE inihibitor or any of the excipients of Tritace
- in patients with a history of angiooedema
- in patients with haemodynamically relevant renal artery stenosis, bilateral or unilateral in the single kidney
- in patients with hypotensive or haemodynamically unstable states
- during pregnancy
- in breast feeding women

4.4 Special warnings and precautions for use

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

Precautions:
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 the majority, 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 haemodialysis.

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: In patients with impaired liver function, response to the treatment with Tritace may be either increased or reduced. In addition, in patients in whom severe liver cirrhosis with oedema and/or ascites is present, the rennin angiotensin system may be significantly activated; therefore, particular caution must be exercised in treating these patients.

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

Patients with hyper stimulated rennin angiotension system: patients are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition. Initial doses or initial dose increases must be accompanied by close blood pressure monitoring until such time as no further acute reduction in blood pressure is to be anticipated. Significant activation of the rennin angiotensin system is to be anticipated, for example: patients with severe malignant hypertension, heart failure, haemodinamically relevant left-ventricular inflow or outflow impediment/renal artery stenosis (discontinuation of diuretic therapy may be required), patients pre-treated with diuretics, patients in whom fluid or salt depletion exists or may develop.
Generally it is recommended that dehydration, hypovolaemia or salt depletion be corrected before initiating treatment (in patients with heart failure, such corrective action must be carefully weighed against the risk of volume overload).

Electrolyte monitoring: It is recommended that serum potassium be monitored regularly. More frequent monitoring of serum potassium is necessary in patients with impaired renal function.

Regular monitoring of serum sodium is recommended in patients undergoing concurrent diuretic therapy.

Patients at risk from a pronounced reduction in blood pressure: In patients who would be at particular risk from an undesirably pronounced reduction in blood pressure (e.g. patients with haemodynamically relevant stenoses of the coronary arteries or of the blood vessels supplying the brain), the initial phase of treatment requires special medical 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 or 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 may a reduction in red cell count, haemoglobin content and platelet count. This is more frequent in patients with renal impairment, especially if they also have collagen vascular disease. No cases of agranulocytosis and neutropenia have been reported to date with Tritace. However, 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.

Angioedema: Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases facial angioedema also occurred. The intestinal angioedema symptoms resolved after stopping the ACE inhibitor.

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 section 4.8 ‘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. b-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.

Vasopressor sympathomimetics: These may reduce the antihypertensive effect of Tritace. Particularly close blood pressure monitoring is recommended.

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

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood picture: Increased likelihood of haematological reactions.

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.

Particularly close blood glucose monitoring is therefore recommended in the initial phase of co-administration.

Concimitant treatment of ACE inhibitors and NSAIDs may lead to an increased risk or worsening of renal function and an increase in serum potassium

If Tritace is given with lithium, an increase in serum lithium concentration may occur. Lithium levels must be monitored.

Heparin: Rise in serum K concentration possible.

Desensitisation therapy: The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venoma is increased under ACE inhibition.

4.6 Pregnancy and lactation

Tritace is contraindicated 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 dilation was observed in the first generation offspring. However, ramipril was not fetotoxic in our studies although ACE inhibitors have shown fetotoxicity in some species.

If the patient becomes pregnant during treatment medication with Tritace must be replaced as soon as possible by a treatment regimen without ACE inhibitors. Otherwise there is a risk of harm to the foetus. Whether exposure limited to the first trimester only can harm the foetus is not known.

Tritace should not be used during lactation.

4.7 Effects on ability to drive and use machines

In individual cases, 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 and Nervous system:
Uncommonly, mild symptoms and reactions such as tachycardia, drowsiness, light-headedness or impaired reactions may occur.
Mild symptoms and reactions such as peripheral oedema, flushing, tinnitus, fatigue, visual disturbances, sweating, disturbed hearing, disturbed orthostatic regulation are rare.

Myocardial infarction or cerebrovascular accident possibly secondary to severe hypotension in high risk patients, chest pain, palpitations, rhythm disturbances, angina pectoris may occur.
Myocardial or cerebral ischaemia, transient ischaemic shock, ischaemic stroke, exacerbation of perfusion disturbances due to vascular stenoses.

Renal: Treatment with Tritace may impair renal function and in isolated cases progression to acute renal failure may occur.

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 or acute liver failure have 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 may 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 syndrome Other skin and mucosal reactions (erythema multiforme, exacerbation of psoriasis, Steven-johnsons syndrome, toxic epidermal necrolysis, psoriasform 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: Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely. 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.

Haematological reactions: In isolated cases, agranulocytosis and pancytopenia and bone marrow depression may occur. In isolated cases, haemolytic anaemia may develop.

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, smell disturbance, 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 (though ACE inhibitors usually reduce proteinuria) or an increase in urinary output may occur.

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

Symptoms: excessive peripheral vasodilation, bradycardia, electrolyte disturbances and renal failure.
Management: In the event of hypotension administration of α_1- adrenergic agonists and angiotensin II (angiotensinamide), must be considered in addition to volume and salt substitution.

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 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 ramiprilat are reached 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 5-10mg ramipril and markedly longer for lower doses, 1.25-2.5mg 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 50%.

5.3 Preclinical safety data

Reproductive 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 foetal 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

Modified starch
Titanium dioxide (E171)
Erythrosine (E127)
Patent blue (E131)
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister, PVC, (calendar) pack of 28 capsules.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi-aventis Ireland Ltd.
Citywest Business Campus
Dublin 24.

8 MARKETING AUTHORISATION NUMBER

PA0540/084/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 March 1989
Date of last renewal: 08 March 2004

10 DATE OF REVISION OF THE TEXT

November 2006