Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ramipril 2.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 2.5 mg ramipril.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet, white, oblong, biplane with facet, both sides with breaking notch.
Embossment one-sided ‘R 2.5’.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension.
Symptomatic heart failure.
Improvement of the prognosis in cardiac failure following myocardial infarction.

4.2 Posology and method of administration

Hypertension:
Recommended initial dose 2.5 mg ramipril once daily. Depending upon patient response the dosage may be increased at intervals of 2-3 weeks initially to 5 mg and then to a maximum dosage of 10 mg once daily or, for therapeutic purposes, a diuretic or calcium channel blocker may be used in combination without increasing the ramipril dosage above 5 mg/day.

Symptomatic heart failure:
Patients with a serious heart disease, hypotension, impaired renal function, electrolyte disturbances or severe cardiac failure should have their treatment initiated in hospital. This also applies to patients who are concomitantly treated with vasodilative agents.

In patients with symptomatic heart failure and in patients receiving diuretic treatment, dose adjustment should take place with care and the recommended initial dose is 1.25 mg daily. This can be increased at intervals of 1-2 weeks to 1.25 mg twice daily and then to 2.5 mg twice daily. The target dose is 10 mg daily. In uncomplicated cases, the treatment can start with 1.25 mg, increased to 1.25 mg twice daily on day 2-7. Week 2: 2.5 mg twice daily. Week 3: 5 mg twice daily. Maintenance treatment can be given as a single dose or divided into two doses.

Improvement of the prognosis in cardiac failure following myocardial infarction:
Therapy is to be initiated in hospital between the third and the tenth day after acute myocardial infarction. The haemodynamic condition should be stable without indications of continuing ischaemia. The initial dosage is 1.25-2.5 mg ramipril twice daily. Blood pressure and renal function should be checked. The dosage is increased after no less than 2 days to 2.5-5 mg ramipril twice daily. The target is 5 mg ramipril twice daily.

Later the daily, initially divided, dosage may be taken as a single daily dose. The maximum dose is 10 mg daily.

If a dosage of 2.5 mg twice daily is not tolerated, withdrawal of treatment is recommended.

In patients receiving diuretic treatment there may sometimes be an excessive fall in blood pressure after the first dose of ramipril. Consequently, diuretic treatment should, if possible, be discontinued 2-3 days before initiation of ramipril therapy. If diuretic treatment is not discontinued, ramipril therapy should be initiated with a 1.25 mg dose once daily, which should then be adjusted according to patient response.

Dosage in patients with impaired renal function:

Creatinine Clearance	Initial dose	Maximum dose
> 50 ml/min	2.5 mg once daily	10 mg once daily
20-50 ml/min	1.25 mg once daily	5 mg once daily
< 20 ml/min	1.25 mg every other day	2.5 mg once daily

Dosage in patients with nephropathy:
Recommended starting dose is 1.25 mg daily. Depending on the blood pressure response and tolerance, the dose can be doubled at intervals of 2-3 weeks. The daily dose should not exceed 10 mg.

Dosage in patients with impaired hepatic function:
In patients with impaired hepatic function, the metabolism of ramipril to biologically active ramiprilat is slowed. This is due to the reduced activity of hepatic esterases, which causes higher concentrations of ramipril in the plasma. Ramipril treatment should therefore be initiated under close medical supervision and the dosage should not exceed 2.5 mg daily.

Use in Elderly
The dose should be in line with the renal function of the elderly patient (see 4.4 Special warnings and special precautions for use, Renal Function Impairment).

Paediatric use
Efficacy and safety of use in children has not been established. Therefore, use in children is not recommended.

Tablets may be divided. They should be swallowed with plenty of liquid and without chewing. Since food does not affect the absorption of Ramipril Tablets, the product may be taken before, during or after a meal.

4.3 Contraindications

- Hypersensitivity to ramipril, to any of the excipients or to any other angiotensin converting enzyme (ACE) inhibitor;
- History of angioedema associated with previous ACE inhibitor therapy;
- Hereditary or idiopathic angioedema;
- Second and third trimesters of pregnancy (see 4.6 “Pregnancy and lactation”).

4.4 Special warnings and precautions for use

Symptomatic Hypotension
Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving ramipril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see 4.5 Interaction with other medicinal products and other forms of interaction and 4.8 Undesirable effects). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an

intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with ramipril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of ramipril may be necessary.

Hypotension In Acute Myocardial Infarction
Treatment with ramipril must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These are patients with systolic blood pressure of 100 mm Hg or lower or those in cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mm Hg or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2.5 mg if systolic blood pressure is 100 mm Hg or lower. If hypotension persists (systolic blood pressure less than 90 mm Hg for more than 1 hour) then ramipril should be withdrawn.

Aortic and Mitral Valve Stenosis / Hypertrophic Cardiomyopathy
As with other ACE inhibitors, ramipril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal Function Impairment
In cases of renal impairment (creatinine clearance <50 ml/min), the initial ramipril dosage should be adjusted according to the patient's creatinine clearance (see 4.2 Posology and Method of Administration, dosage in patients with impaired renal function) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of ramipril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ramipril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or ramipril may be required.

In acute myocardial infarction, treatment with ramipril should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177 micromol/l and/or proteinuria exceeding 500 mg/24 h. If renal dysfunction develops during treatment with ramipril (serum creatinine concentration exceeding 265 micromol/l or a doubling from the pre-treatment value) then the physician should consider withdrawal of ramipril.

Haemodialysis Patients
Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Hypersensitivity/Angioedema
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including ramipril. This may occur at any time during therapy. In such cases, ramipril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the

tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see 4.3 Contraindications).

Anaphylactoid Reactions During Low-Density Lipoproteins (LDL) Apheresis
Rarely, patients receiving ACE inhibitors during low-density lipoproteins (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Desensitisation
Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

Hepatic Failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Neutropenia/ Agranulocytosis
Neutropenia/ Agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Ramipril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If ramipril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Race
Angiotensin converting enzyme inhibitors cause a 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 patients than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

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.

Surgery/Anaesthesia
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, ramipril 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.

Hyperkalaemia
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including ramipril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see 4.5 Interaction with other medicinal products and other forms of interaction).

Diabetic Patients
In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see 4.5 Interaction with other medicinal products and other forms of interaction).

Lithium
The combination of lithium and ramipril is generally not recommended (see 4.5 Interaction with other medicinal products and other forms of interaction).

Pregnancy and Lactation
Ramipril should not be used during the first trimester of pregnancy. Ramipril is contraindicated in the second and third trimesters of pregnancy (see 4.3 Contraindications). When pregnancy is detected, ramipril treatment should be discontinued as soon as possible (see 4.6 Pregnancy and lactation).

Use of ramipril is not recommended during breast feeding.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions with other substances or materials should be taken into account when using these at the same time as ramipril.

Potassium Sparing Diuretics or Potassium Supplements
ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. If concomitant use is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium (see 4.4 Special warnings and special precautions for use).

Diuretics (thiazide or loop diuretics)
Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with ramipril (see 4.4 Special warnings and special precautions for use). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of ramipril.

Other Antihypertensive Agents
Concomitant use of these agents may increase the hypotensive effects of ramipril. Concomitant use with nitroglycerine and other nitrates, or other vasodilators, may further reduce blood pressure.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors. Use of ramipril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see 4.4).

Tricyclic Antidepressants/Antipsychotics/Anesthetics/Narcotics
Concomitant use of certain anesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE

inhibitors may result in further reduction of blood pressure (see 4.4 Special warnings and special precautions for use).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Chronic administration of NSAID's may reduce the antihypertensive effect of an ACE inhibitor.

NSAID's and ACE inhibitors exert an additive on the increase in serum potassium, and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as the elderly or dehydrated.

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

4.6 Pregnancy and lactation

Pregnancy
Ramipril should not be used during the first trimester of pregnancy. When pregnancy is planned or confirmed the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but a limited number of cases with first trimester toxicity exposure have not appeared to manifest malformations consistent with human foetotoxicity as described below.

Ramipril is contraindicated during the second and third trimester of pregnancy.

Prolonged ACE inhibitor exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia (see also 5.3 Preclinical safety data).

Should exposure to ramipril have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended.

Infants whose mothers have taken ramipril should be closely observed for hypotension, oliguria and hyperkalaemia. Ramipril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Lactation
It is not known whether ramipril is excreted into human breast milk. Ramipril is excreted into the milk of lactating rats. The use of ramipril is not recommended in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

A fall in blood pressure may impair the patient's ability to concentrate and react and thus, for example, the ability to drive a car and operate machines. The effect is more intense at the beginning of treatment and in combination with alcohol.

4.8 Undesirable effects

The following undesirable effects have been observed during treatment with ramipril and other ACE inhibitors with the following frequencies: Very common (≥10%), common (≥1%,<10%), uncommon (≥0.1%, <1%), rare (≥0.01%,<0.1%), very rare (<0.01%) including isolated reports.

Blood and the lymphatic system disorders:

rare:	decreases in haemoglobin, decreases in haematocrit.
very rare:	bone marrow depression, anaemia, thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia, lymphadenopathy, autoimmune disease.

Metabolism and nutrition disorders

very rare:	hypoglycaemia.

Nervous system and psychiatric disorders:

common:	dizziness, headache.
uncommon:	mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances.
rare:	mental confusion.

Cardiac and vascular disorders:

common:	orthostatic effects (including hypotension).
uncommon:	myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see 4.4 Special warnings and precautions for use), palpitations, tachycardia, chest pain, angina pectoris, Raynaud's phenomenon.

Respiratory, thoracic and mediastinal disorders:

common:	cough.
uncommon:	rhinitis.
very rare:	bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorders:

common:	diarrhoea, vomiting.
uncommon:	nausea, abdominal pain and indigestion.
rare:	dry mouth.
very rare:	pancreatitis, hepatitis- either hepatocellular or cholestatic, jaundice, intestinal angioedema.

Skin and subcutaneous tissue disorders:

uncommon:	rash, pruritus.
rare:	hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported rarely (see 4.4 Special warnings and precautions for use), urticaria, alopecia, psoriasis.
very rare:	diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme.

A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity, onycholysis or other dermatological manifestations may occur.

Renal and urinary disorders:

common:	renal dysfunction.
rare:	uraemia, acute renal failure.
very rare:	oliguria/anuria.

Reproductive system and breast disorders:

uncommon:	impotence.
rare:	gynaecomastia.

General disorders and administration site conditions:

uncommon:	fatigue, asthenia.

Investigations:

uncommon:	increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia.
rare:	increases in serum bilirubin, hyponatraemia.

4.9 Overdose

The following symptoms may for example occur: severe hypotension, shock, electrolyte imbalance and renal failure. The treatment given depends upon the amount of the agent taken and the time of administration, and upon the symptoms manifested and their severity. Unabsorbed ramipril should be eliminated (e.g. by gastric lavage, adsorbents, sodium sulphate; if possible during the first 30 minutes).

Vital functions should be monitored in intensive care and should, if necessary, be supported. In hypotension the administration of catecholamines and angiotensin II should be considered in addition to the correction of blood volume and salt deficiency. No data are available relating to the effectiveness of intensified diuresis, alteration of urinary pH, haemofiltration or dialysis for the purpose of accelerating the elimination of ramipril or ramiprilat. If dialysis or haemofiltration is considered, see the section 4.3 “Contraindications”.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-Code: C09AA05.

Mechanism of action: Ramiprilat, the active metabolite of ramipril, inhibits the activity of the angiotensin-converting enzyme. In the plasma and tissues this enzyme catalyses the conversion of angiotensin I to the active angiotensin II which causes vasoconstriction and it inhibits the breakdown of the active vasodilator bradykinin. The reduced formation of angiotensin II and inhibition of the breakdown of bradykinin lead to vasodilation. Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a fall in aldosterone secretion. The increase in the activity of bradykinin possibly promotes heart-protecting and endothelium-protecting effects, which have been observed in animal tests. To what extent this is the cause of certain adverse effects (such as irritability) is still not known.

Following the administration of ramipril there is a significant fall of peripheral arterial pressure. In general the renal perfusion and glomerular filtration rate do not alter significantly.

In hypertensives ramipril lowers the blood pressure in both supine and standing position without increasing the heart rate in compensation. In most patients the antihypertensive effect commences 1 - 2 hours after a single dose and is most intense 3 - 6 hours after taking the preparation. The effect lasts for 24 hours after a single dose. The maximal blood pressure response is usually achieved after 3 - 4 weeks regular treatment. It has been demonstrated that the antihypertensive effect is retained in long-term therapy (2 years). Sudden termination of ramipril treatment does not cause a rapid and steep rise in blood pressure.

5.2 Pharmacokinetic properties

Ramipril is a prodrug that undergoes intensive first pass metabolism in the liver, which is essential for the formation of ramiprilat, the active metabolite of the substance (hydrolysis occurs principally in the liver). As a result of the activation/metabolism of this prodrug, the bioavailability of an oral dose of ramipril is approximately 20 %.

Of a 10 mg orally administered and radioactively labelled dose of ramipril, approximately 40 % is excreted in the faeces and 60 % in the urine.

Ramipril is absorbed rapidly after an oral dose.

Food intake does not significantly affect the absorption of ramipril.

The peak serum concentration of ramiprilat is reached 2 - 4 hours after an oral dose of ramipril.

The half-life is 13 - 17 hours after a repeated dose. The distribution volume is approximately 500 l. The protein binding of ramiprilat is approximately 56 %. In healthy volunteers aged 65 - 76 years the pharmacokinetic properties of ramiprilat correspond to those found in healthy young volunteers.

Renal excretion of ramipril decreases in patients with renal impairment and the renal clearance of ramiprilat correlates with the creatinine clearance. This leads to a rise in plasma concentrations of ramiprilat. The concentrations fall more slowly than in persons with normal renal function.

When using large doses (10 mg) of ramipril hepatic impairment reduces the activation of ramipril from ramipril to ramiprilat, which leads to elevated ramipril concentrations and reduces the elimination of ramiprilat.

Neither in healthy volunteers nor in hypertensive patients, including those suffering from cardiac failure, any significant accumulation of ramipril or ramiprilat was found when 5 mg ramipril was given orally once daily for two weeks.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Reproductive toxicity studies suggest that ramipril has no effects on fertility and reproductive performance in rats, and is not teratogenic. In a study in which female rats were dosed prior to mating through gestation, an increased incidence of rat pup deaths occurred during lactation. The compound has been shown to cross the placenta and is secreted in milk. Angiotensin converting enzyme inhibitors, as a class, have been shown to be foetotoxic (causing injury and/or death to the foetus) when given in the second or third trimester.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Microcrystalline cellulose
Pregelatinised starch
Sodium hydrogen carbonate
Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

24 months.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container

The tablets are packed in aluminium/aluminium blisters and inserted in a carton, or packed in a HDPE bottle with a dessicant in the cap.

Original packages containing 14, 20, 28, 30, 50, 98, 100, 250 tablets.
Not all pack sizes and types of container may be marketed.

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

None.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co. Cork

8 MARKETING AUTHORISATION NUMBER

PA 711/105/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 December 2005

10 DATE OF REVISION OF THE TEXT

February 2006