Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ramic 1.25 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 1.25mg ramipril.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard
Size 4, light grey capsule body and cap, marked R on cap and 1.25 on body, containing a white or almost white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

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

Ramic 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. Ramic 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. Ramic 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. Ramic capsules should be taken with plenty of liquid. The absorption of Ramic is not affected by food.

Hypertension
The recommended initial dose in patients not on diuretics and without congestive heart failure is 2.5mg Ramic 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 Ramic as a single dose. If the patient response is still unsatisfactory at the maximum dose of 10mg Ramic, combination treatment is recommended.

Diuretic treated patients
The diuretic should be discontinued 2-3 days before beginning therapy with Ramic to reduce the likelihood of symptomatic hypotension. If the diuretic cannot be discontinued, the initial dose of Ramic should be 1.25mg.

Dosage adjustment in renal impairment
The usual dose of Ramic is recommended for patients with a creatinine clearance >30 ml/min (serum creatinine < 165 micromol/l) for patients with creatinine clearance <30 ml/min (serum creatinine > 165 micromol/l), the initial dosage is 1.25mg Ramic once daily and the maximum dose 5mg Ramic once daily. In patients with severe renal impairment (creatinine clearance <10 ml/min and serum creatinine of 400-650 micromol/l), the recommended initial dose is also 1.25mg Ramic once a day, but the maintenance dosage should not exceed 2.5mg Ramic 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 to a diminished activity of esterases in the liver, resulting in elevated plasma Ramipril levels. Treatment with Ramic should therefore be initiated with a reduced dose under close medical supervision in patients with impaired hepatic 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
Ramic 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 before starting Ramic.

Post myocardial infarction
Initiation of therapy:
Treatment must be started in hospital between day 3 and day 10 following Acute Myocardial Infarction (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.

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 Angiotensin Converting Enzyme (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 Ramic 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 Ramic. 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 Ramic, or at least to reducing the diuretic dose.

In patients with impaired liver function, the response to treatment with Ramic 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 Ramic.

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 2.5mg Ramic 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 10mg. The usual maintenance dose is 10mg Ramic daily.

Prevention of myocardial infarction, stroke or cardiovascular death in type 2 diabetic patients with an increased cardiovascular risk
The recommended initial dose is 2.5mg Ramic 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 10mg. The usual maintenance dose is 10mg Ramic daily.

Prevention of progression of microalbuminuria to overt nephropathy
The recommended initial dose is 2.5mg Ramic 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 10mg. The usual maintenance dose is 10mg Ramic daily.

4.3 Contraindications

Hypersensitivity to Ramipril.

Use in patients with a history of angioneurotic oedema relating to previous treatment with an ACE inhibitor.

Second and third trimesters of pregnancy (see section 4.4 and 4.6).

Use in children.

4.4 Special warnings and precautions for use

Warnings:
Ramic 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 Ramic; 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 Ramic is given, in particular concomitantly with a diuretic. Dosage reduction of Ramic 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).

Symptomatic hypotension:
In patients with uncomplicated hypertension, symptomatic hypotension has been observed rarely after the initial dose of Ramipril as well as after increasing the dose of Ramipril. 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 Ramic.

Surgery/Anaesthesia:
In patients undergoing surgery or during anaesthesia with agents producing hypotension, Ramic may block angiotensin II formation secondary to compensatory rennin 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 Ramic.

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.

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 Ramic. 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.

Pregnancy: ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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, alternate therapy should be started (see sections 4.3 and 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of ACE inhibitors and antidiabetic medicines (insulin, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with the risk of hypoglycaemia. This phenomenon may be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see section 4.3 and 4.4).

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 antihypertensive 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.
Exposure to ACE inhibitor therapy 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 section 5.3.) Should exposure to ACE inhibitors 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 sections 4.3 and 4.4).

Lactation
Because insufficient information is available regarding the use of ramipril during breastfeeding (see section 5.2), Ramic is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

In individual cases, treatment with Ramic 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 Ramic and after an increase in the dose of Ramic.

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. Syncopy has been observed rarely.

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

Renal:
Treatment with Ramic may impair renal function.

Gastrointestinal:
Treatment with Ramic 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 may resolve spontaneously after withdrawal of Ramic.

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 (maculopapular and lichenoid exanthema and enanthema), sometimes pronounced hair loss, and precipitation or intensification of Raynaud's syndrome.

Other skin and mucosal reactions (erythema multiforme, 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 Ramic 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, terror, 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 pre-treated with a diuretic. Pre-existing proteinuria may deteriorate.

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 rennin 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, 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 Ramipril 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 24 hours after a single daily dose.

Data indicate no loss of effect during long terms 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%.

Lactation:
One single 10 mg oral dose of ramipril produced an undetectable level in breast milk. However the effect of multiple doses is not known.

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 female rats during the foetal period and lactation produced irreversible renal damage (dilatation of the renal pelvis) in the offspring at daily doses of 50mg/kg body weight and higher.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised Starch
Gelatin
Black iron oxide (E172)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

15 months.

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Al/Al Blister Strips.

Pack sizes: 7, 21, 28, 30, 50 and 100 capsules.

Not all pack sizes 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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Limited
Ballymacarbry
Clonmel
Co. Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 281/119/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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