IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0126/156/003
Case No: 2013554

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

Clonmel Healthcare Limited

Waterford Road, **Clonmel**, **Co. Tipperary**, **Ireland**

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

Ramitace 5 mg 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 **19/05/2006** until **18/05/2011**.

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

Ramitace 5 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 5 mg Ramipril.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

Light grey gelatin capsules, marked with “R” on the cap and “5” on the body.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For reducing the risk of myocardial infarction, stroke, cardiovascular mortality or need for revascularisation procedures in patients of 55 years or more who have clinical evidence of cardiovascular disease (previous MI, unstable angina or multivessel CABG or multivessel PTCA), stroke or peripheral vascular disease.

Also for reducing the risk of myocardial infarction, stroke, cardiovascular mortality or need for revascularisation procedures in diabetic patients of 55 years or more who have one or more of the following clinical findings: hypertension (systolic blood pressure> 160mmHg or diastolic blood pressure> 90mmHg); high total cholesterol >5.2 mmol/L); low HDL (<0.9 mmol/L); current smoker; known microalbuminuria; clinical evidence of previous vascular disease.

Ramipril is indicated for the treatment of mild to moderate hypertension.

4.2 Posology and method of administration

Dosage and Administration:

Ramipril capsules should be taken orally with a glass of water. The absorption of ramipril is not affected by food.

Reducing the risk of myocardial infarction, stroke or cardiovascular mortality and/or the need for revascularisation procedures: The recommended initial dose is 2.5mg Ramipril once a day. Depending on the tolerability, the dose should be gradually increased. It is therefore recommended that this dose is doubled after about one week of treatment then, after a further 3 weeks, it should be finally increased to 10mg. The usual maintenance dose is 10mg Ramipril once a day.

Patients already stabilised on lower doses of ramipril for other indications where possible should be titrated to 10mg Ramipril once daily.

Hypertension: The recommended initial dosage in patients not on diuretics and without congestive heart failure is 1.25 mg to 2.5 mg 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 is 2.5 - 5 mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 10 mg Ramipril, combination treatment is recommended.

In diuretic treated patients, the diuretic should be discontinued 2 - 3 days before beginning therapy with ramipril to reduce the likelihood of symptomatic hypotension. It may be resumed later if required. Where diuretic therapy cannot be discontinued or is restarted, therapy should be initiated with the lowest single dose of 1.25 mg Ramipril.

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 1.25 mg under close medical supervision in hospital.

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

In patients with severe renal impairment (creatinine clearance < 10 ml/min and serum creatinine of 400-650 μmol/l), the recommended initial dose is also 1.25 mg Ramipril once a day, but the maintenance dose should not exceed 2.5 mg Ramipril once a day.
If creatinine clearance cannot be measured it can be calculated from serum creatinine concentration using the Cockroft formula.

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 delayed due to a diminished activity of esterases in the liver, resulting in elevated plasma ramipril levels. Treatment with ramipril should therefore be initiated at a dose of 1.25 mg once a day; the total daily dose must not exceed 2.5 mg ramipril. Patients with impaired liver function should be kept under close medical supervision.

Elderly: Caution in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to need for the control of blood pressure

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

4.3 Contraindications

Hypersensitivity to ramipril, any of its excipients or to any other ACE inhibitor
Hereditary or idiopathic angioneurotic oedema
Haemodynamically relevant stenosis of the renal arteries bilaterally, or unilaterally in the case of single kidney
Hypotensive or haemodynamically unstable patients
During pregnancy and lactation

4.4 Special warnings and precautions for use

***Warnings*:**

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.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism generally do not respond to antihypertensives with a mode of action based on inhibition of the renin-angiotensin system. Therefore, ramipril should not be used in these patients.

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

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 section 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

Patients with renal insufficiency may require reduced or less frequent doses of ramipril; 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.

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 immediately and the patient closely monitored. Even in those instances where only swelling of 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 (0.5 mg of 1:1000) 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 angiodema while receiving an ACE inhibitor (see also "Contraindications"). Other hypersensitivity reactions have been reported,

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 ACE inhibitors.

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.

Patients with hepatic impairment may have an impaired capacity to form the active metabolite ramiprilat. There is not enough experience to give definite dose recommendations.

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 section 4.5 Interaction with other medicinal products and other forms of interaction and section 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.

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.

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.

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.

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 medicinal products 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 section Interaction with other medicinal products and other forms of interaction).

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.

Race
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.

Children/dialysis patients/severe cardiac insufficiency after myocardial infarction
There is insufficient experience of the use of ramipril for children, for dialysis patients and for patients with severe cardiac insufficiency after myocardial infarction.

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.

Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to ramipril.

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 section 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.

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 section 4.4 Special warnings and special precautions for use).

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

Ganglionic and adrenergic-blocking drugs should only be combined with ramipril under careful supervision.

Antidiabetics
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic 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.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor. NSAIDs and ACE inhibitors exert an additive effect 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

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 risk of 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

Tricyclic antidepressants / Antipsychotics /Anaesthetics / Narcotics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4 Special warnings and precautions for use).

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

Vasopressor Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors. Particularly close blood pressure monitoring is recommended.

Heparin
Increased serum potassium concentrations can be expected (see section 4.4 Special warnings and precautions for use).

Desensitisation therapy: the likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom is increased under ACE inhibition. It is assumed that this effect may also occur in connection with other allergens.

Alcohol
Ramipril may potentiate the effect of alcohol.

Salt
The increased use of salt (sodium) may impair the antihypertensive effect of ramipril.

4.6 Pregnancy and lactation

Pregnancy should be excluded before start of treatment with ramipril 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 foetotoxic in studies although ACE inhibitors have shown foetotoxicity in some species. ramipril 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 ramipril 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

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.

Cardiac and vascular disorders:
*Commo*n: orthostatic effects (including hypotension), (syncope, chest pain, angina pectoris)
uncommon: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see 4.4 Special warning and precautions for use), palpitations, tachycardia, Raynaud's phenomenon

Renal and urinary disorders:
Common: renal dysfunction
Rare: uraemia, acute renal failure
Very rare: oliguria/anuria

Gastrointestinal disorders:
Common: diarrhoea, vomiting
*Uncommo*n: nausea, abdominal pain and indigestion, anorexia
Rare: dry mouth
Very rare: pancreatitis, hepatitis- either hepatocellular or cholestatic, jaundice, intestinal angioedema, billiary cirrhosis.

Skin and subcutaneous tissue disorders:
Uncommon: rash, pruritus
Rare: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see section 4.4 Special warning 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 or other dermatological manifestations may occur.

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

Respiratory, thoracic and mediastinal disorders:
Common: cough
Uncommon: rhinitis, dyspnoea
Very rare: bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia

Blood and the lymphatic system disorders:
Rare: decreases in haemoglobin, decreases in haematocrit
Very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia (possibly related to G6PDH deficiency), lymphadenopathy, autoimmune disease

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

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

Eye disorders:
Increased myopia

Reproductive system and breast disorders:
Uncommon: impotence
Rare: gynaecomastia

Investigations:
Uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia
Rare: increases in serum bilirubin, hyponatraemia.

General disorders and administration site conditions:
Uncommon: fatigue, asthenia
*Very rare***:** 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.

4.9 Overdose

In case of overdosage the following symptoms may occur: severe hypotension, shock, bradycardia, disturbance in the electrolyte balance and renal insufficiency. Treatment will depend on the amount of medicinal product taken, on the time of administration, and on the type and severity of symptoms. Unabsorbed ramipril must be eliminated (e.g. by gastric lavage, the administration of adsorbing agents such as, sodium sulphate or activated charcoal, during the first 30 minutes, if possible).

Vital signs should be carefully monitored and supported in an intensive care setting. In the event of hypotension vasoconstrictor catecholamines should be administered and if necessary the administration of angiotensin II might be considered. Blood volume and salt depletion should also be corrected. Bradycardia should be treated with atropine. There is no experience on the efficacy of forced diuresis, adjustment of urinary pH, haemofiltration or dialysis in accelerating the elimination of ramipril.
Whenever haemofiltration or haemodialysis are used the section 4.4 “Special warnings and precautions for use” should be taken into consideration. Haemodialysis is usually not required except if needed for other reasons such as renal failure.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C09A A05

Agents acting on Renin-angiotensin system, ACE inhibitors, plain.

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 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 ramipril appears to have some effects on the kallikrein-kinin-prostaglandin systems. It is assumed that effects on these systems contribute to the hypotensive 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 therapeutic doses.

In a large endpoint study – HOPE – ramipril significantly reduced the incidence of stroke, myocardial infarction and/or cardiovascular death when compared with placebo. These benefits occurred largely in normotensive patients and were shown, using standard regression analysis techniques, to be only partially due to the relatively modest reductions in blood pressure demonstrated in the study. The 10mg dose, currently the highest safe dose level approved, was selected by the HOPE investigators from previous dose-ranging studies (SECURE, HEART) and was considered to be the most likely dose to effect full blockade of the rennin-angiotensin-aldosterone system. This and other studies suggest that ACE inhibitors like ramipril are likely to have other direct effects on the cardiovascular system. These may include the antagonism of angiotensin II mediated vasoconstriction, the inhibition of proliferating vascular smooth muscle and plaque rupture, the enhancement of endothelial function, the reduction of LV hypertrophy and positive effects on fibrinolysis. Additional effects in diabetic patients may also contribute e.g. effects on insulin clearance and pancreatic blood flow.

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.

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

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.

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 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

Capsule filling:
Pregelatinised starch

Capsule shell:
Gelatin
Titanium Dioxide (E171)
Black Iron Oxide (E172)
Yellow Iron Oxide (E172)
Indigo Carmine FD & C Blue 2 (E132)

Printing Ink:
Shellac Glaze – 47.5%
Black Iron Oxide
Soya Lecithin
Antifoam DC 1510

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

18 months

6.4 Special precautions for storage

Do not store above 25 °C.
Store in the original packaging.

6.5 Nature and contents of container

Al/Al Blister pack.

Pack sizes: 7, 21, 28, 30, 50, 100 capsules.
*Not all 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

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 126/156/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19th May 2006

10 DATE OF REVISION OF THE TEXT