IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0967/006/001
Case No: 2064661

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

Ranbaxy (UK) Limited

20 Balderton Street, **London W1K 6TL**, **United Kingdom**

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

Bellramil, 1.25 Milligram

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 **19/05/2009** until **26/07/2012**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bellramil 1.25 mg Capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains ramipril 1.25 mg.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, hard, Size 4 with yellow cap/white body imprinted with ‘R’ on cap and ‘1.25’ on body. Contains white to off-white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For reducing the risk of myocardial infarction, stroke, cardiovascular death 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 death 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 Capsules are indicated for the treatment of mild to moderate hypertension.

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

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

4.2 Posology and method of administration

Dosage and Administration:

Oral administration

Reducing the risk of myocardial infarction, stroke or cardiovascular death 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 ramipril 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.

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.

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

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

Post myocardial infarction:

Initiation of therapy: Treatment must be started in hospital between day 3 and day 10 following myocardial infarction. The starting dose is 2.5 mg twice a day during 2 days. Depending upon the patient’s response to the therapy the dose may be increased to 5 mg twice a day after 1 to 3 day interval. If the initial 2.5 mg dose is not tolerated, a dose of 1.25 mg twice a day should be given for two days before increasing to 2.5 mg and 5 mg twice a day. If the dose cannot be increased to 2.5 mg twice a day, treatment should be withdrawn. Maximum daily dose is 10 mg. Maintenance dose: 2.5 mg - 5 mg twice a day.’

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.

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 under close medical supervision in patients with impaired liver function.

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.

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

Maximum daily dose should not exceed 2.5 mg in patients with hepatic impairment.

4.3 Contraindications

Hypersensitivity to ramipril or any of the excipients.

History of angioneurotic oedema

Haemodynamically relevant renal artery stenosis (bilateral or unilateral in single kidney). Ramipril should not be used in patients with aortic or mitral valve stenosis of outflow obstruction.

Hypotensive or haemodynamically unstable patients.

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

4.4 Special warnings and precautions for use

Warnings:
Ramipril should not be used in patients with aortic or mitral valve 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 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. If recognised early, such impairment of renal function is reversible upon discontinuation of therapy.

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

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

Some hypertensive patients with no apparent pre-existing renal disease, may develop minor and usually transient increases in blood urea nitrogen and serum creatinine when ramipril is given, in particular concomitantly with a diuretic. Dosage reduction of ramipril 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, vomiting or 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 ramipril.

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 ramipril may usually be continued following restoration of effective blood volume and blood pressure.

Surgery/anaesthesia: In patients undergoing surgery or during anaesthesia with agents producing 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 appropriate treatment.

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

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, alternative therapy should be started (see sections 4.3 and 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to ramipril. Adrenergic-blocking drugs should only be combined with ramipril under careful supervision.

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

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

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

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

Patients on allopurinol, immunosuppressants and other substances that may change the blood picture also have increased likelihood of other blood picture changes.

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

4.6 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 sections 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), ramipril 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, 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

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

Blood and lymphatic disorders Very rare, including isolated cases Rare	 Agranulocytosis and bone marrow depression Reduction in red blood cell count and haemoglobin content, reduction in the white blood cell or blood platelet count
Immune system disorders Common Rare	 Hypertensitivity reactions accompanied by pruritus, rash, shortness of breath, fever may occur, Eosinophilia. Raised titres of antinuclear antibodies Angioneurotic oedema
Psychiatric disorders Common	 Sleep disorders, Depressed mood, feeling of anxiety
Nervous system disorders Common	 Dizziness, disturbances of balance, nervousness, restlessness, tremor, confusion, loss of appetite, paraesthesiae.
Eye disorders Common	 Conjunctivitis
Cardiac disorders	

Common Rare	Symptomatic hypotension accompanied by dizziness, weakness and nausea 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.
Common	Syncope Myocardial infraction or cerebrovascular accident possibly secondary to severe hypotension, chest pain, palpitations, rhythm disturbances, angina pectoris
Vascular disorders Common	 Vasculitis
Respiratory, thoracic and mediastinal disorders Common	 Dry tickling cough Rhinitis, sinusitis, bronchitis and especially in patients with tickling cough, bronchspasm
Gastrointestinal disorders Common Rare	 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
Skin and aubcutaneous tissue disorder Common	 Cutaneous and mucosal reactions: reddening of skin areas with accompanying heat sensation, itching, urticaria, other skin or mucosal eruptions (maculo-papular and lichenoid exanthema and enanthema, erythema multiforme), sometimes pronounced hair loss, and precipitation or intensification of Raynaud's phenomenon. With other ACE inhibitors psoriasiform and pemphigoid exanthema and enanthema, hypersensitivity of the skin to light and onycholysis
Musculoskeletal and connective tissue disorders Common	Muscle cramps, muscle and joint pains
Renal and urinary disorders	Impair renal function.

Common	
Reproductive system and breast disorders Common	Impotence, decreased libido
General disorders and administration site conditions Common	Taste change, taste reduction and sometimes loss of taste, Fever, headache, fatigue, malaise
Investigations Common	Increases in blood urea nitrogen and serum creatinine may occur, in particular with renal insufficiency or in patients pretreated with a diuretic. Pre-existing proteinuria may deteriorate. Serum sodium levels may decrease. Elevation of serum potassium may occur, since ramipril leads to a decrease in aldosterone secretion; potassium-sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements should therefore be avoided.

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

ATC-code: C09A A05

The pharmacotherapeutic group: 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 renin activity and a decrease in plasma concentrations of angiotensin II and aldosterone. The beneficial haemodynamic effects resulting from ACE inhibition are a consequence of the reduction in angiotensin II causing dilatation of peripheral vessels and reduction in vascular resistance. There is evidence suggesting that tissue ACE particularly in the vasculature, rather than circulating ACE, is the primary factor determining the haemodynamic effects.

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

Administration of 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.

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 renin-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 left ventricular 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.

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Pregelatinised starch (Maize)

Capsules Shell
Yellow cap / White body, size ‘4

Cap Shell
Gelatin
Quinoline yellow (E 104)
Ponceau 4R (E 124)
Titanium dioxide (E 171)

Printing Ink
Shellac
Propylene glycol

Potassium hydroxide
Black iron oxide (E 172)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

2 Years

6.4 Special precautions for storage

Store in the original packeage.

6.5 Nature and contents of container

Aluminium strips comprising of aluminium foil laminated with LDPE. The strips are enclosed in a cardboard carton in pack sizes of 21, 28, 30, 56 or 60 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

Ranbaxy (UK) Limited
20 Balderton Street
London W1K 6TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 967/6/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th July 2007

10 DATE OF REVISION OF THE TEXT

May 2009