

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Bellramil 10 mg Capsules, hard

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains ramipril 10 mg.

For a full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Capsule, hard,. Size 4 with blue cap/white body imprinted with 'R' on cap and '10' on body. Contains white to off-white granular powder.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

- Treatment of hypertension.
- Cardiovascular prevention: reduction of cardiovascular morbidity and mortality in patients with:
  - o manifest atherothrombotic cardiovascular disease (history of coronary heart disease or stroke, or peripheral vascular disease) or
  - o diabetes with at least one cardiovascular risk factor (see section 5.1).
- Treatment of renal disease:
  - o Incipient glomerular diabetic nephropathy as defined by the presence of microalbuminuria,
  - o Manifest glomerular diabetic nephropathy as defined by macroproteinuria in patients with at least one cardiovascular risk factor (see section 5.1),
  - o Manifest glomerular non diabetic nephropathy as defined by macroproteinuria  $\geq 3$  g/day (see section 5.1).
- Treatment of symptomatic heart failure.
- Secondary prevention after acute myocardial infarction: reduction of mortality from the acute phase of myocardial infarction in patients with clinical signs of heart failure when started > 48 hours following acute myocardial infarction.

### 4.2 Posology and method of administration

Oral use

It is recommended that Bellramil is taken each day at the same time of the day.

Bellramil can be taken before, with or after meals, because food intake does not modify its bioavailability (see section 5.2). Bellramil has to be swallowed with liquid. It must not be chewed or crushed.

AdultsDiuretic-Treated patients

Hypotension may occur following initiation of therapy with Bellramil; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.

If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Bellramil (see section 4.4).

In hypertensive patients in whom the diuretic is not discontinued, therapy with Bellramil should be initiated with a 1.25 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Bellramil should be adjusted according to blood pressure target.

*Hypertension*

The dose should be individualised according to the patient profile (see section 4.4) and blood pressure control.

Bellramil may be used in monotherapy or in combination with other classes of antihypertensive medicinal products.

*Starting dose*

Bellramil should be started gradually with an initial recommended dose of 2.5 mg daily.

Patients with a strongly activated renin-angiotensin-aldosterone system may experience an excessive drop in blood pressure following the initial dose. A starting dose of 1.25 mg is recommended in such patients and the initiation of treatment should take place under medical supervision (see section 4.4).

*Titration and maintenance dose*

The dose can be doubled at interval of two to four weeks to progressively achieve target blood pressure; the maximum permitted dose of Bellramil is 10 mg daily. Usually the dose is administered once daily.

Cardiovascular prevention*Starting dose*

The recommended initial dose is 2.5 mg of Bellramil once daily.

*Titration and maintenance dose*

Depending on the patient's tolerability to the active substance, the dose should be gradually increased. It is recommended to double the dose after one or two weeks of treatment and - after another two to three weeks - to increase it up to the target maintenance dose of 10 mg Bellramil once daily.

See also posology on diuretic treated patients above.

Treatment of renal disease*In patients with diabetes and microalbuminuria:**Starting dose:*

The recommended initial dose is 1.25 mg of Bellramil once daily.

*Titration and maintenance dose*

Depending on the patient's tolerability to the active substance, the dose is subsequently increased. Doubling the once daily dose to 2.5 mg after two weeks and then to 5 mg after a further two weeks is recommended.

In patients with diabetes and at least one cardiovascular risk*Starting dose:*

The recommended initial dose is 2.5 mg of Bellramil once daily.

*Titration and maintenance dose*

Depending on the patient's tolerability to the active substance, the dose is subsequently increased. Doubling the daily dose to 5 mg Bellramil after one or two weeks and then to 10 mg Bellramil after a further two or three weeks is recommended. The target daily dose is 10 mg.

In patients with non- diabetic nephropathy as defined by macroproteinuria >3 g/day.*Starting dose:*

The recommended initial dose is 1.25 mg of Bellramil once daily.

*Titration and maintenance dose*

Depending on the patient's tolerability to the active substance, the dose is subsequently increased. Doubling the once daily dose to 2.5 mg after two weeks and then to 5 mg after a further two weeks is recommended.

Symptomatic heart failure*Starting dose*

In patients stabilized on diuretic therapy, the recommended initial dose is 1.25 mg daily.

*Titration and maintenance dose*

Bellramil should be titrated by doubling the dose every one to two weeks up to a maximum daily dose of 10 mg. Two administrations per day are preferable.

Secondary prevention after acute myocardial infarction and with heart failure*Starting dose*

After 48 hours, following myocardial infarction in a clinically and haemodynamically stable patient, the starting dose is 2.5 mg twice daily for three days. 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 the treatment should be withdrawn.

See also posology on diuretic treated patients above.

*Titration and maintenance dose*

The daily dose is subsequently increased by doubling the dose at intervals of one to three days up to the target maintenance dose of 5 mg twice daily.

The maintenance dose is divided in 2 administrations per day where possible.

If the dose cannot be increased to 2.5 mg twice a day treatment should be withdrawn. Sufficient experience is still lacking in the treatment of patients with severe (NYHA IV) heart failure immediately after myocardial infarction. Should the decision be taken to treat these patients, it is recommended that therapy be started at 1.25 mg once daily and that particular caution be exercised in any dose increase.

Special populations*Patients with renal impairment*

Daily dose in patients with renal impairment should be based on creatinine clearance (see section 5.2):

- if creatinine clearance is  $\geq 60$  ml/min, it is not necessary to adjust the initial dose (2.5 mg/day); the maximal daily dose is 10 mg;
- if creatinine clearance is between 30-60 ml/min, it is not necessary to adjust the initial dose (2.5 mg/day); the maximal daily dose is 5 mg;
- if creatinine clearance is between 10-30 ml/min, the initial dose is 1.25 mg/day and the maximal daily dose is 5 mg;
- in haemodialysed hypertensive patients: Bellramil is slightly dialysable; the initial dose is 1.25 mg/day and the maximal daily dose is 5 mg; the medicinal product should be administered few hours after haemodialysis is performed.

Patients with hepatic impairment (see section 5.2)

In patients with hepatic impairment, treatment with Bellramil must be initiated only under close medical supervision and the maximum daily dose is 2.5 mg Bellramil.

#### *Elderly*

Initial doses should be lower and subsequent dose titration should be more gradual because of greater chance of undesirable effects especially in very old and frail patients. A reduced initial dose of 1.25 mg Bellramil should be considered.

#### *Paediatric population*

The safety and efficacy of ramipril in children has not yet been established. Currently available data for Ramipril are described in sections 4.8, 5.1, 5.2 & 5.3 but no specific recommendation on posology can be made.

### **4.3 Contraindications**

Hypersensitivity to Bellramil, to any of the excipients (listed in section 6.1) or any other ACE (Angiotensin Converting Enzyme) inhibitors (see section 6.1).

History of angioneurotic oedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or AIIRAs)

Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5).

Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney.

Ramipril must not be used in 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**

#### Special populations

- *Pregnancy*: ACE inhibitors such as Bellramil, or Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued ACE inhibitor/ AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors/ AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

- *Patients at particular risk of hypotension*

- *Patients with strongly activated renin-angiotensin-aldosterone system*

Patients with strongly activated renin-angiotensin-aldosterone system are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition, especially when an ACE inhibitor or a concomitant diuretic is given for the first time or at first dose increase.

Significant activation of renin-angiotensin-aldosterone system is to be anticipated and medical supervision including blood pressure monitoring is necessary, for example in:

- patients with severe hypertension

- patients with decompensated congestive heart failure

- patients with haemodynamically relevant left ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve)
- patients with unilateral renal artery stenosis with a second functional kidney
- patients in whom fluid or salt depletion exists or may develop (including patients with diuretics)
- patients with liver cirrhosis and/or ascites
- patients undergoing major surgery or during anaesthesia with agents that produce hypotension.

Generally, it is recommended to correct dehydration, hypovolaemia or salt depletion before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed out against the risk of volume overload).

- *Transient or persistent heart failure post MI*
- *Patients at risk of cardiac or cerebral ischemia in case of acute hypotension*

The initial phase of treatment requires special medical supervision.

- *Elderly patients*

See section 4.2.

- *Surgery*

It is recommended that treatment with angiotensin converting enzyme inhibitors such as Bellramil should be discontinued where possible one day before surgery.

- *Monitoring of renal function*

Renal function should be assessed before and during treatment and dosage adjusted especially in the initial weeks of treatment. Particularly careful monitoring is required in patients with renal impairment (see section 4.2). There is a risk of impairment of renal function, particularly in patients with congestive heart failure or after a renal transplant.

- *Angioedema*

Angioedema has been reported in patients treated with ACE inhibitors including Bellramil (see section 4.8).

In case of angioedema, Bellramil must be discontinued.

Emergency therapy should be instituted promptly. Patient should be kept under observation for at least 12 to 24 hours and discharged after complete resolution of the symptoms.

Intestinal angioedema has been reported in patients treated with ACE inhibitors including Bellramil (see section 4.8). These patients presented with abdominal pain (with or without nausea or vomiting).

- *Anaphylactic reactions during desensitization*

The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom and other allergens are increased under ACE inhibition. A temporary discontinuation of Bellramil should be considered prior to desensitization.

*- Hyperkalaemia*

Hyperkalaemia has been observed in some patients treated with ACE inhibitors including Bellramil. Patients at risk for development of hyperkalaemia include those with renal insufficiency, age (> 70 years), uncontrolled diabetes mellitus, or those using potassium salts, potassium retaining diuretics and other plasma potassium increasing active substances, or conditions such as dehydration, acute cardiac decompensation, metabolic acidosis. If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

*Neutropenia/agranulocytosis*

Neutropenia/agranulocytosis, as well as thrombocytopenia and anaemia, have been rarely seen and bone marrow depression has also been reported. It is recommended to monitor the white blood cell count to permit detection of a possible leucopenia. More frequent monitoring is advised in the initial phase of treatment and in patients with impaired renal function, those with concomitant collagen disease (e.g. lupus erythematosus or scleroderma), and all those treated with other medicinal products that can cause changes in the blood picture (see sections 4.5 and 4.8).

*Ethnic differences*

ACE inhibitors cause higher rate of angioedema in black patients than in non black patients.

As with other ACE inhibitors, Bellramil may be less effective in lowering blood pressure in black people than in non black patients, possibly because of a higher prevalence of hypertension with low renin level in the black hypertensive population.

*Cough*

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

**4.5 Interaction with other medicinal products and other forms of interaction***Contra-indicated combinations*

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

*Precautions for use*

*Potassium salts, heparin, potassium-retaining diuretics and other plasma potassium increasing active substances (including Angiotensin II antagonists, trimethoprim, tacrolimus, ciclosporin):* Hyperkalaemia may occur, therefore close monitoring of serum potassium is required.

*Antihypertensive agents (e.g. diuretics) and other substances that may decrease blood pressure (e.g. nitrates, tricyclic antidepressants, anaesthetics, acute alcohol intake, baclofen, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin):* Potentiation of the risk of hypotension is to be anticipated (see section 4.2 for diuretics)

*Vasopressor sympathomimetics and other substances (e.g. isoproterenol, dobutamine, dopamine, epinephrine) that may reduce the antihypertensive effect of Bellramil:* Blood pressure monitoring is recommended.

*Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood cell count:* Increased likelihood of haematological reactions (see section 4.4).

*Lithium salts:* Excretion of lithium may be reduced by ACE inhibitors and therefore lithium toxicity may be increased. Lithium level must be monitored.

*Antidiabetic agents including insulin:* Hypoglycaemic reactions may occur. Blood glucose monitoring is recommended.

*Non-steroidal anti-inflammatory drugs and acetylsalicylic acid:* Reduction of the antihypertensive effect of Bellramil is to be anticipated. Furthermore, concomitant treatment of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and to an increase in kalaemia.

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

Bellramil is not recommended during the first trimester of pregnancy (see section 4.4) and contraindicated during the second and third trimesters of pregnancy (see section 4.3).

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/Angiotensin II Receptor Antagonist (AIIRA) 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. Newborns whose mothers have taken ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia (see sections 4.3 and 4.4).

### Breastfeeding

Because insufficient information is available regarding the use of Bellramil during breastfeeding (see section 5.2), Bellramil 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

Some adverse effects (e.g. symptoms of a reduction in blood pressure such as dizziness) may impair the patient's ability to concentrate and react and, therefore, constitute a risk in situations where these abilities are of particular importance (e.g. operating a vehicle or machinery).

This can happen especially at the start of treatment, or when changing over from other preparations. 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 safety profile of Bellramil includes persistent dry cough and reactions due to hypotension. Serious adverse reactions include angioedema, hyperkalaemia, renal or hepatic impairment, pancreatitis, severe skin reactions and neutropenia/agranulocytosis.

Adverse reactions frequency is defined using the following convention:

Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

	Common	Uncommon	Rare	Very rare	Not known
<u>Blood and lymphatic system disorders</u>		Eosinophilia	White blood cell count decreased (including neutropenia or agranulocytosis), red blood cell count decreased, haemoglobin decreased, platelet count decreased		Bone marrow failure, pancytopenia, haemolytic anaemia
<u>Immune system disorders</u>					Anaphylactic or anaphylactoid reactions, antinuclear antibody increased
<u>Metabolism and nutrition disorders</u>	Blood potassium increased	Anorexia, decreased appetite			Blood sodium decreased
<u>Psychiatric disorders</u>		Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence	Confusional state		Disturbance in attention
<u>Nervous system disorders</u>	Headache, dizziness	Vertigo, paraesthesia, ageusia, dysgeusia,	Tremor, balance disorder		Cerebral ischaemia including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired, burning sensation, parosmia
<u>Eye disorders</u>		Visual disturbance including blurred vision	Conjunctivitis		
<u>Ear and labyrinth disorders</u>			Hearing impaired, tinnitus		
<u>Cardiac disorders</u>		Myocardial ischaemia including angina pectoris or myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral			
<u>Vascular disorders</u>	Hypotension, orthostatic blood pressure decreased,	Flushing	Vascular stenosis, hypoperfusion, vasculitis		Raynaud's phenomenon

	syncope				
<u>Respiratory, thoracic and mediastinal disorders</u>	Non-productive tickling cough, bronchitis, sinusitis, dyspnoea	Bronchospasm including asthma aggravated, nasal congestion			
<u>Gastrointestinal disorders</u>	Gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting	Pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, constipation, dry mouth	Glossitis		Aphthous stomatitis
<u>Hepatobiliary disorders</u>		Hepatic enzymes and/or bilirubin conjugated increased			Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very rarely exceptional)
<u>Skin and subcutaneous tissue disorders</u>	Rash in particular maculo-papular	Angioedema; very exceptionally, the airway obstruction resulting from angioedema may have a fatal outcome; pruritus, hyperhidrosis	Exfoliative dermatitis, urticaria, onycholysis,	Photosensitivity reaction	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia
<u>Musculoskeletal and connective tissue disorders</u>	Muscle spasms, myalgia	Arthralgia			
<u>Renal and urinary disorders</u>		Renal impairment including renal failure acute, urine output increased, worsening of a pre-existing proteinuria, blood urea increased blood creatinine increased			
<u>Reproductive system and breast disorders</u>		Transient erectile impotence, libido decreased			Gynaecomastia

General disorders and administration site conditions

Chest pain, fatigue

Pyrexia

Asthenia

### Paediatric Population

The safety of ramipril was monitored in 325 children and adolescents, aged 2-16 years old during 2 clinical trials. Whilst the nature and severity of the adverse events are similar to that of the adults, the frequency of the following is higher in the children:

Tachycardia, nasal congestion and rhinitis, “common” (i.e.  $\geq 1/100$  to  $< 1/10$ ) in paediatric, and “uncommon” (i.e.  $\geq 1/1,000$  to  $< 1/100$ ) in adult population.

Conjunctivitis “common” (i.e.  $\geq 1/100$  to  $< 1/10$ ) in paediatric while “rare” (i.e.  $\geq 1/10,000$  to  $< 1/1,000$ ) in adult population.

Tremor and urticaria “uncommon” (i.e.  $\geq 1/1,000$  to  $< 1/100$ ) in paediatric population while “rare” (i.e.  $\geq 1/10,000$  to  $< 1/1,000$ ) in adult population.

The overall safety profile for ramipril in paediatric patients dose not differ significantly from the safety profile in adults.

## **4.9 Overdose**

Symptoms associated with overdosage of ACE inhibitors may include excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure. The patient should be closely monitored and the treatment should be symptomatic and supportive. Suggested measures include primary detoxification (gastric lavage, administration of adsorbents) and measures to restore haemodynamic stability, including, administration of alpha 1 adrenergic agonists or angiotensin II (angiotensinamide) administration. Ramiprilat, the active metabolite of Bellramil is poorly removed from the general circulation by haemodialysis.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

The pharmacotherapeutic group: ACE Inhibitors, plain, ATC-code C09A A05

#### Mechanism of action

Ramiprilat, the active metabolite of the prodrug Bellramil, inhibits the enzyme dipeptidylcarboxypeptidase I (synonyms: angiotensin-converting enzyme; kininase II). In plasma and tissue this enzyme catalyses the conversion of angiotensin I to the active vasoconstrictor substance angiotensin II, as well as the breakdown of the active vasodilator bradykinin. Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilatation.

Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in aldosterone secretion. The average response to ACE inhibitor monotherapy was lower in black (Afro-Caribbean) hypertensive patients (usually a low-renin hypertensive population) than in non-black patients.

#### Pharmacodynamic effects

Antihypertensive properties:

Administration of Bellramil causes a marked reduction in peripheral arterial resistance. Generally, there are no major changes in renal plasma flow and glomerular filtration rate. Administration of Bellramil to patients with hypertension leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate.

In most patients the onset of the antihypertensive effect of a single dose becomes apparent 1 to 2 hours after oral administration. The peak effect of a single dose is usually reached 3 to 6 hours after oral administration. The antihypertensive effect of a single dose usually lasts for 24 hours.

The maximum antihypertensive effect of continued treatment with Bellramil is generally apparent after 3 to 4 weeks. It has been shown that the antihypertensive effect is sustained under long term therapy lasting 2 years.

Abrupt discontinuation of Bellramil does not produce a rapid and excessive rebound increase in blood pressure.

#### Heart failure:

In addition to conventional therapy with diuretics and optional cardiac glycosides, Bellramil has been shown to be effective in patients with functional classes II-IV of the New-York Heart Association. The drug had beneficial effects on cardiac haemodynamics (decreased left and right ventricular filling pressures, reduced total peripheral vascular resistance, increased cardiac output and improved cardiac index). It also reduced neuroendocrine activation.

#### Clinical efficacy and safety

##### Cardiovascular prevention/Nephroprotection:

A preventive placebo-controlled study (the HOPE-study), was carried out in which Bellramil was added to standard therapy in more than 9,200 patients. Patients with increased risk of cardiovascular disease following either atherothrombotic cardiovascular disease (history of coronary heart disease, stroke or peripheral vascular disease) or diabetes mellitus with at least one additional risk factor (documented microalbuminuria, hypertension, elevated total cholesterol level, low high-density lipoprotein cholesterol level or cigarette smoking) were included in the study.

The study showed that Bellramil statistically significantly decreases the incidence of myocardial infarction, death from cardiovascular causes and stroke, alone and combined (primary combined events).

##### **The HOPE Study: Main Results;**

	Bellramil	Placebo	relative risk (95% confidence interval)	p-value
	%	%		
<b>All patients</b>	<b>n=4,645</b>	<b>N=4,652</b>		
<b>Primary combined events</b>	<b>14.0</b>	<b>17.8</b>	<b>0.78 (0.70-0.86)</b>	<b>&lt;0.001</b>
<i>Myocardial infarction</i>	9.9	12.3	0.80 (0.70-0.90)	<0.001
<i>Death from cardiovascular causes</i>	6.1	8.1	0.74 (0.64-0.87)	<0.001
<i>Stroke</i>	3.4	4.9	0.68 (0.56-0.84)	<0.001
<b>Secondary endpoints</b>				
<i>Death from any cause</i>	10.4	12.2	0.84 (0.75-0.95)	0.005
<i>Need for Revascularisation</i>	16.0	18.3	0.85 (0.77-0.94)	0.002
<i>Hospitalisation for unstable angina</i>	12.1	12.3	0.98 (0.87-1.10)	NS
<i>Hospitalisation for heart failure</i>	3.2	3.5	0.88 (0.70-1.10)	0.25
<i>Complications related to diabetes</i>	6.4	7.6	0.84 (0.72-0.98)	0.03

The MICRO-HOPE study, a predefined substudy from HOPE, investigated the effect of the addition of Bellramil 10 mg to the current medical regimen versus placebo in 3,577 patients at least  $\geq 55$  years old (with no upper limit of age), with a majority of type 2 diabetes (and at least another CV risk factor), normotensive or hypertensive.

The primary analysis showed that 117 (6.5 %) participants on Bellramil and 149 (8.4 %) on placebo developed overt nephropathy, which corresponds to a RRR 24 %; 95 % CI [3-40],  $p = 0.027$ .

The REIN study, a multicenter randomized, double-blind parallel group, placebo-controlled study aimed at assessing the effect of treatment with Bellramil on the rate of decline of glomerular function rate (GFR) in 352 normotensive or hypertensive patients (18-70 years old) suffering from mild (i.e. mean urinary protein excretion  $> 1$  and  $< 3$  g/24 h) or severe proteinuria ( $\geq 3$  g/24 h) due to chronic non-diabetic nephropathy. Both subpopulations were prospectively stratified.

The main analysis of patients with the most severe proteinuria (stratum prematurely disrupted due to benefit in Bellramil group) showed that the mean rate of GFR decline per month was lower with Bellramil than with placebo;  $-0.54$  (0.66) vs.  $-0.88$  (1.03) ml/min/month,  $p = 0.038$ . The intergroup difference was thus  $0.34$  [0.03-0.65] per month, and around 4 ml/min/year; 23.1 % of the patients in the Bellramil group reached the combined secondary endpoint of doubling of baseline serum creatinine concentration and/or end-stage renal disease (ESRD) (need for dialysis or renal transplantation) vs. 45.5 % in the placebo group ( $p = 0.02$ ).

#### Secondary prevention after acute myocardial infarction

The AIRE study included more than 2,000 patients with transient/persistent clinical signs of heart failure after documented myocardial infarction. The Bellramil treatment was started 3 to 10 days after the acute myocardial infarction. The study showed that after an average follow-up time of 15 months the mortality in Bellramil-treated patients was 16.9 % and in the placebo treated patients was 22.6 %. This means an absolute mortality reduction of 5.7 % and a relative risk reduction of 27 % (95 % CI [11-40 %]).

#### Paediatric Population

In a randomized, double-blind, placebo-controlled clinical study involving 244 paediatric patients with hypertension (73% primary hypertension), aged 6-16 years, patients received either low dose, medium dose or high dose of ramipril to achieve plasma concentrations of ramiprilat corresponding to the adult dose range of 1.25mg, 5mg and 20mg on the basis of body weight. At the end of 4 weeks, ramipril was ineffective in the endpoint of lowering systolic blood pressure but lowered diastolic blood pressure at the highest dose. Both medium and high doses of Ramipril showed significant reduction of both systolic and diastolic blood pressure in children with confirmed hypertension.

This effect was not seen in a 4 week dose-escalation, randomized, double-blind withdrawal study in 218 paediatric patients aged 6-16 years (75% primary hypertension), where both diastolic and systolic blood pressures demonstrated a modest rebound but not a statistically significant return to the baseline, in all three dose levels tested [low dose (0.625mg – 2.5mg), medium dose (2.5mg – 10mg) or high dose (5mg – 20mg)] ramipril based on weight. Ramipril did not have a linear dose response in the paediatric population studied.

## **5.2 Pharmacokinetic properties**

### Pharmacokinetics and Metabolism

#### Absorption

Following oral administration Bellramil is rapidly absorbed from the gastrointestinal tract: peak plasma concentrations of Bellramil are reached within one hour. Based on urinary recovery, the extent of absorption is at least 56 % and is not significantly influenced by the presence of food in the gastrointestinal tract. The bioavailability of the active metabolite ramiprilat after oral administration of 2.5 mg and 5 mg Bellramil is 45 %.

Peak plasma concentrations of ramiprilat, the sole active metabolite of Bellramil are reached 2-4 hours after Bellramil intake. Steady state plasma concentrations of ramiprilat after once daily dosing with the usual doses of Bellramil are reached by about the fourth day of treatment.

### Distribution

The serum protein binding of Bellramil is about 73 % and that of ramiprilat about 56 %.

### Metabolism

Bellramil is almost completely metabolised to ramiprilat, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of Bellramil and ramiprilat.

### Elimination

Excretion of the metabolites is primarily renal.

Plasma concentrations of ramiprilat decline in a polyphasic manner. Because of its potent, saturable binding to ACE and slow dissociation from the enzyme, ramiprilat shows a prolonged terminal elimination phase at very low plasma concentrations.

After multiple once-daily doses of Bellramil, the effective half-life of ramiprilat concentrations was 13-17 hours for the 5-10 mg doses and longer for the lower 1.25-2.5 mg doses. This difference is related to the saturable capacity of the enzyme to bind ramiprilat.

A single oral dose of Bellramil produced an undetectable level of Bellramil and its metabolite in breast milk. However the effect of multiple doses is not known.

Patients with renal impairment (see section 4.2)

Renal excretion of ramiprilat is reduced in patients with impaired renal function, and renal ramiprilat clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of ramiprilat, which decrease more slowly than in subjects with normal renal function.

Patients with hepatic impairment (see section 4.2)

In patients with impaired liver function, the metabolism of Bellramil to ramiprilat was delayed, due to diminished activity of hepatic esterases, and plasma Bellramil levels in these patients were increased. Peak concentrations of ramiprilat in these patients, however, are not different from those seen in subjects with normal hepatic function.

### Lactation

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

### Paediatric Population

The pharmacokinetic profile of ramipril was studied in 30 paediatric hypertensive patients, aged 2-16 years, weighing  $\geq$  10kg. After doses of 0.05 to 0.2mg/kg, ramipril was rapidly and extensively metabolized to ramiprilat. Peak plasma concentrations of ramiprilat occurred within 2-3 hours. Ramiprilat clearance highly correlated with the log of body weight ( $p < 0.01$ ) as well as dose ( $p < 0.001$ ). Clearance and volume of distribution increased with increasing children age for each dose group. The dose of 0.05mg/kg in children achieved exposure levels comparable to those in adults treated with ramipril 5mg. The dose of 0.2mg/kg in children resulted in exposure levels higher than the maximum recommended dose of 10mg per day in adults.

## 5.3 Preclinical safety data

Oral administration of Bellramil has been found to be devoid of acute toxicity in rodents and dogs.

Studies involving chronic oral administration have been conducted in rats, dogs and monkeys.

Indications of plasma electrolyte shifts and changes in blood picture have been found in the 3 species.

As an expression of the pharmacodynamic activity of Bellramil, pronounced enlargement of the juxtaglomerular apparatus has been noted in the dog and monkey from daily doses of 250 mg/kg/d.

Rats, dogs and monkeys tolerated daily doses of 2, 2.5 and 8 mg/kg/d respectively without harmful effects.

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 Bellramil 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 or higher.

Extensive mutagenicity testing using several test systems has yielded no indication that Bellramil possesses mutagenic or genotoxic properties.

Irreversible kidney damage has been observed in very young rats given a single dose of ramipril.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule contents

Pregelatinised starch (Maize)

#### Capsules Shell

Blue cap / White body, size '4

#### Cap Shell

Gelatin

Patent blue (E131)

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 package.

### **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 and other handling**

Any unused product or waste material should be disposed of in accordance with local requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Ranbaxy Ireland Limited

Spafield

Cork Road

Cashel  
Co. Tipperary

**8 MARKETING AUTHORISATION NUMBER**

PA 0408/092/003

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 27<sup>th</sup> July 2007

**10 DATE OF REVISION OF THE TEXT**

December 2013