Safeguarding public health

MHRA

# Public Assessment Report

# Mutual Recognition Procedure

## Ramipril 1.25, 2.5, 5 & 10 mg Capsules

**MRP no: UK/H/795/01-04**
**UK licence no: PL 06831/0102-5**

**Applicant: Genus Pharmaceuticals Limited**

# Ramipril 1.25mg Capsules
# Ramipril 2.5mg Capsules
# Ramipril 5mg Capsules
# Ramipril 10mg Capsules

## LAY SUMMARY

Austria, Belgium, Czech Republic, Hungary, Ireland, Luxembourg, and Slovakia today granted Genus Pharmaceuticals Ltd Marketing Authorisations (licences) for the medicinal products Ramipril 1.25mg Capsules (PL 06831/0102) Ramipril 2.5mg Capsules (PL 06831/0103), Ramipril 5mg Capsules (PL 06831/0104) and Ramipril 10mg Capsules (PL 06831/0105). These are prescription-only medicines (POM) to help lower blood pressure if too high (mild to moderate hypertension) and to prevent the heart getting weaker if you have recently suffered a heart attack. These can also be used to reduce the risk of heart attack, stroke, need for surgical procedure to increase blood flow to heart and to reduce risk to patients with diabetes and at least one clinical finding (elevated blood pressure, high cholesterol, smoking or previously suffering a heart condition) in patients over 55 years of age.

Ramipril Capsules contain the active ingredient ramipril, which belongs to a group of drugs called angiotensin converting enzyme (ACE) inhibitors, which act on the heart and blood vessels.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Ramipril 1.25mg, 2.5mg, 5mg and 10mg Capsules outweigh the risks, hence Marketing Authorisations have been granted.

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# Module 1

| | |
|---|---|
| **Product Name** | Ramipril capsules |
| **Type of Application** | 1.25mg:<br>Abridged<br>Initial application<br>Generic, Article 10.1(a)(iii)<br>Chemical substance<br>Prescription only<br><br>2.5mg, 5mg, 10mg:<br>Abridged<br>Additional strength<br>Generic, Article 10.1(a)(iii)<br>Chemical substance<br>Prescription only |
| **Active Substance** | Ramipril Ph. Eur. |
| **Form** | Capsule |
| **Strength** | 1.25, 2.5, 5 & 10 mg |
| **MA Holder** | Genus Pharmaceuticals Ltd |
| **RMS** | United Kingdom |
| **CMS** | Austria, Belgium, Czech Republic, Hungary, Ireland, Luxembourg, and Slovakia. |
| **Procedure Number** | UK/H/795/01-04 |
| **Timetable** | Day 90 15/11/2005 |

# Module 2

## SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Ramipril XX mg Capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains XX mg Ramipril

For excipients, see ***section*** 6.1.

## 3. PHARMACEUTICAL FORM

Capsule, hard

Light grey gelatin capsules; marked with “R” on the cap and “XX” 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 measures it can be calculated form 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 angioedema 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 hypoglycemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycemia. 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 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 /Anesthetics / Narcotics***

Concomitant use of certain anesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see 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, leukopenia.

***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 fetal 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 fetotoxic in studies although ACE inhibitors have shown fetotoxicity in some species.
Ramipril should not be used during lactation.
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**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:***
*common*: 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, biliary 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 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 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 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 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 een identified, including diketopiperazine ester, diketopiperazine acid and conjugates.
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## 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

*Ramipril 1.25mg - Capsule filling:*
Pregelatinised starch.
*Capsule shell:*
Gelatin
Titanium Dioxide (E171)
Black Iron Oxide (E172)
**Printing Ink:**
Shellac Glaze – 47.5%
Black Iron Oxide
Soya Lecithin
Antifoam DC 1510

*Ramipril 2.5, 5 & 10 mg - 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

Ramipril 1.25 mg Capsules -18 months
Ramipril 2.5 mg Capsules - 24 months
Ramipril 5 mg Capsules - 24 months
Ramipril 10 mg Capsules - 24 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 Instructions for use and handling and disposal**

No special requirements

**7. MARKETING AUTHORISATION HOLDER**

**8. MARKETING AUTHORISATION NUMBERS**

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

**10. DATE OF REVISION OF THE TEXT**

# Module 3

# Product Information Leaflet

PATIENT INFORMATION LEAFLET

## Lopace® 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules (Ramipril)

**What you should know about Lopace Capsules**
Please read this carefully before you start to take your medicine. This leaflet provides a summary of the information available on your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist. This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
The name of your medicine is Lopace 1.25 mg, 2.5 mg, 5 mg, or 10 mg Capsules.

**What is in your medicine?**
The active substance in your Lopace Capsules is ramipril. The capsules are available in four strengths. The 1.25 mg capsules are light grey in colour, with "R" marked on the capsule cap and "1.25" on the capsule body. The 2.5 mg capsules have a light green cap marked "R" and a light grey capsule body marked "2.5". The 5 mg capsules have a green cap marked "R" and a light gray capsule body marked "5". The 10 mg capsules have a dark green cap marked "R" and a light gray capsule body marked "10".
Each capsule contains 1.25 mg, 2.5 mg, 5 mg, or 10 mg of ramipril, the active ingredient. The other ingredients are starch (pregelatinised), gelatin and the colourings, black iron oxide (E172) and titanium dioxide (E171). The 2.5 mg, 5 mg and 10 mg capsules also contain the colourings indigo carmine (E132) and yellow iron oxide (E172). The printing ink on the capsules contains the following additional ingredients: shellac, soya lecithin and antifoam.
The capsules are supplied in blister packs of 28 capsules.
Ramipril is one of a group of medicines called ACE (angiotensin converting enzyme) inhibitors. These work by widening blood vessels which makes it easier for the heart to pump blood through them, to all parts of the body. This helps to reduce raised blood pressure. It can also help the heart to work better if the heart does not pump as well as is needed.
**The Product Licence holder is:** Genus Pharmaceuticals, Benham Valence, Newbury, Berkshire RG20 8LU, United Kingdom.
**The manufacturer is:** Actavis hf., Reykjavikurvegur 78, IS-220 Hafnarfjördur, Iceland.

**Uses**
Your doctor has probably prescribed these capsules for one of the following reasons:
- To reduce the risk of a heart attack and heart disease, to decrease the risk of requiring a surgical procedure to increase the blood flow to the heart and to reduce your chance of having a stroke. This applies to 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.
- In diabetic patients, of 55 years or more, who show symptoms of high blood pressure, high cholesterol, peripheral vascular disease, have known microalbuminuria (small amounts of a protein called albumin in the urine), or are smokers. In these patients, these capsules can reduce the risk of heart attack, heart disease and stroke and decreases the risk of requiring surgery to increase blood flow to the heart.
- To lower mild to moderately high blood pressure.

**Before taking your medicine**
Do not take these capsules if:
- you are hypersensitive (allergic) to ramipril or any of the other ingredients listed above
- you are pregnant
- you are breast-feeding
- you have a history of the condition known as angioneurotic oedema
- you have kidney problems which affect your heart rate
- you have low or changing blood pressure
- you have been told by your doctor that you have any of the following heart conditions; aortic valve stenosis, mitral valve stenosis or outflow obstruction.

Take special care with these capsules if:
- you have heart problems or if you have any kidney or liver disease. Your doctor may need to monitor you and change the dose of your medicine.
- you are on haemodialysis using high flux polyacrylonitrile (AN69) membranes. Inform your doctor of this so a different technique can be chosen to prevent hypersensitivity reactions.
- you take a high dose of diuretic medication (water tablets).
- you have lupus erythematosus or scleroderma.
- you are taking any medications which may affect your blood picture, your doctor can advise you of this.
- you need an operation or an anaesthetic, tell the doctor or dentist that you are taking Lopace Capsules.
- you are taking medication for low potassium levels.
- you are taking diuretic medication (water tablets). Your doctor may discontinue diuretic therapy and correct volume and/or salt depletion before starting treatment with ramipril.
- you are taking allopurinol and/or other immunosuppressants as this may increase the likelihood of blood picture changes.

Pregnancy:
Ask your doctor or pharmacist for advice before taking any medicine.
Lopace Capsules should not be taken if you are pregnant or think you may be pregnant, as the capsules could harm the unborn baby.
Breast-feeding:
Ask your doctor or pharmacist for advice before taking any medicine.
Lopace Capsules should not be taken by women who are breast-feeding.
Driving and using machines:
It is not advisable to drive or operate machinery for several hours after the first dose of capsules or after an increase in dose.
You should not drive or operate machinery if you feel dizzy or tired while taking these capsules.
Drinking alcohol may make the dizziness or sleepiness worse.
Using other medicines:
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.
You should especially inform your doctor if you have been taking any of the following:
- diuretics (water tablets) particularly potassium sparing diuretics
- medicines for high blood pressure
- medicines for diabetes
- lithium

Discovery

- non steroidal anti-inflammatory drugs (NSAIDs)
- treatment for gout
- corticosteroids
- drugs to depress the immune system
- medicines containing potassium.

**Taking your medicine**

Always follow your doctor's instructions as to how and when to take your medicine. your pharmacist may be able to advise you if you are not sure. Exactly how many capsules, and how often you must take them, will be written on the label. Please read it carefully. The recommended doses are given below. However, doctors sometimes prescribe different doses to these: if this applies to you, discuss it with your doctor, if you have not already done so.

Swallow the capsules whole with a glass of water. Take the dose at approximately the same time each day.

Adults and elderly patients over 65 years:

*Reducing the risk of heart attack, stroke and the need for surgery to improve blood flow to your heart:* the usual starting dose is one 2.5 mg capsule once a day. This dose will gradually be increased by your doctor. After three weeks of treatment the dose is usually 10 mg once a day.

*Hypertension (high blood pressure):* the usual starting dose for patients is one 1.25 mg capsule once a day. Your doctor may decide to increase the dose after one to two weeks of treatment. Most people with hypertension need doses of 2.5 mg or 5 mg once a day, but your doctor may decide you need a different dose, up to a maximum of 10 mg once a day.

If you are taking diuretic medications (water tablets) then your doctor may decide to reduce the dose before starting treatment with Lopace Capsules.

Kidney Disease: For patients with kidney disease (renal impairment with creatinine clearance less than 30 ml/min), the initial dose of ramipril is usualy 1.25 mg once daily. This may be increased to 2.5 mg or 5 mg once daily depending on the type of kidney disease.

Liver Problems: For patients with liver problems, treatment with ramipril is usually started at a dose of 1.25 mg once daily under close medical supervision.

Elderly: If you are elderly and taking water tablets or have heart, kidney or liver problems your doctor may start your treatment with a low dose of ramipril and increase it if needed.

Children: Lopace Capsules are not recommended for use in children.

If you wish to stop treatment, discuss this with your doctor first as your original symptoms will return.

If you have the impression that the effect of these capsules is too strong or too weak, talk to your doctor or pharmacist.

If you have forgotten to take your medicine, take the missed dose as soon as you remember, unless it is nearly time for the next dose. Do not double the next dose to make up for the missed one. If you are at all concerned about this you should consult your doctor or pharmacist.

If you have taken too many capsules, contact your doctor or local hospital accident and emergency department immediately. You may experience low blood pressure which will result in dizziness.

**After taking your medicine**

Lopace Capsules may cause unwanted effects in some people. The most common of these effects include feeling sick, dizziness and headache. Other possible, but less common, side effects are described below.

*Blood Circulation:* low blood pressure with dizziness, weakness and feeling sick. Fainting. Rare reports of chest pain, fast or changing heart beat and angina.

*Kidney Problems:* in some people ramipril may affect the kidneys. Pre-existing proteinuria (elevated protein levels in the urine) may deteriorate.

*Gastrointestinal:* dry mouth, irritation or swelling in the mouth, stomach pains, diarrhoea or constipation, feeling or being sick, changes in liver enzymes (including jaundice). Rare reports of pancreatitis (inflammation of the pancreas).

*Allergic Reactions:* itchy skin, rash, shortness of breath and sometimes fever.

*Skin:* reddening of skin areas with accompanying heat sensation, conjunctivitis (eye infection), pronounced hair loss and reduced circulation to the hands and/or feet (Raynaud's phenomenon). As with other medicines of this type (i.e. ACE inhibitors) sensitivity of the skin to light and effects on the nails (loosening) has been observed.

*Respiratory tract:* dry tickling cough, bronchitis, and a runny or stuffy nose.

*Angioneurotic oedema:* in very rare cases this condition has occurred which includes symptoms such as swelling of the face, tongue and throat.

*Other Effects:* disturbance of balance, headache, nervousness, restlessness, tremor, problems with sleeping, confusion, loss of appetite, depressed mood, feeling of anxiety, pins and needles, muscle cramps, muscle and joint pains, fever, vasculitis (inflammation of the blood vessels), sexual inability in men, and reduced sexual desire (libido). A very small number of people find that this medicine affects their sense of taste.

Blood tests may show an increase in some liver test results. An increase in blood urea nitrogen, creatinine levels, serum potassium levels and a decrease in serum sodium levels may also be observed. Taking ramipril may result in an increase in the number of so-called eosinophilic blood cells.

Tell your doctor at once if:

- you feel ill after your first dose (a few people may react to their first dose and feel very dizzy, weak, faint and sick)
- you get a lot of infections with sore throats or mouth ulcers
- you notice a rash, skin eruption or other effects on your skin or eyes, itching or a high temperature
- you notice swelling of the face, tongue or throat.

Ask your doctor if you should continue taking the capsules.

**Stop taking Lopace Capsules immediately and go to your doctor or casualty department if:**

- your breathing becomes difficult and noisy
- you get any swelling of the face, tongue or throat.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

**Storing your medicine**

Do not take this medicine after the expiry date stated on the carton. Any out of date medicines should be returned to your pharmacist for disposal. If you notice any visible signs of deterioration in the capsules, take them to your pharmacist for advice before taking them.

Unused capsules should be taken back to the pharmacist for safe disposal.

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

Keep out of the reach and sight of children. REMEMBER this medicine is for you. Only a doctor can prescribe it for you. Never give it to others, it may harm them even if their symptoms are the same as yours.

This leaflet applies to Lopace Capsules 1.25 mg, 2.5 mg, 5 mg, and 10 mg only.

Date of preparation: September 2004.

**Distributed by:** Discovery Pharmaceuticals, The Old Vicarage, Market Place, Castle Donington, Derbyshire. DE74 2JB

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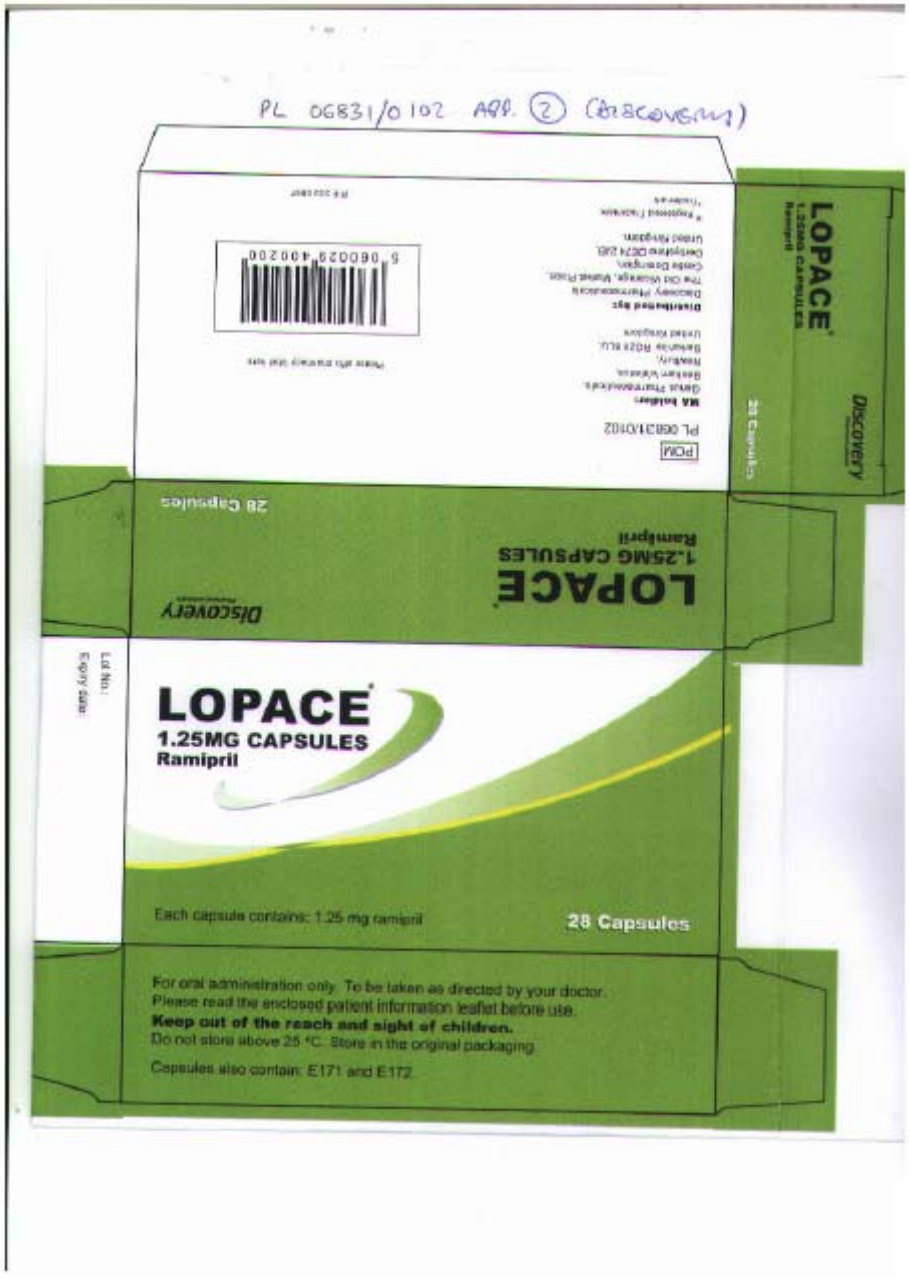
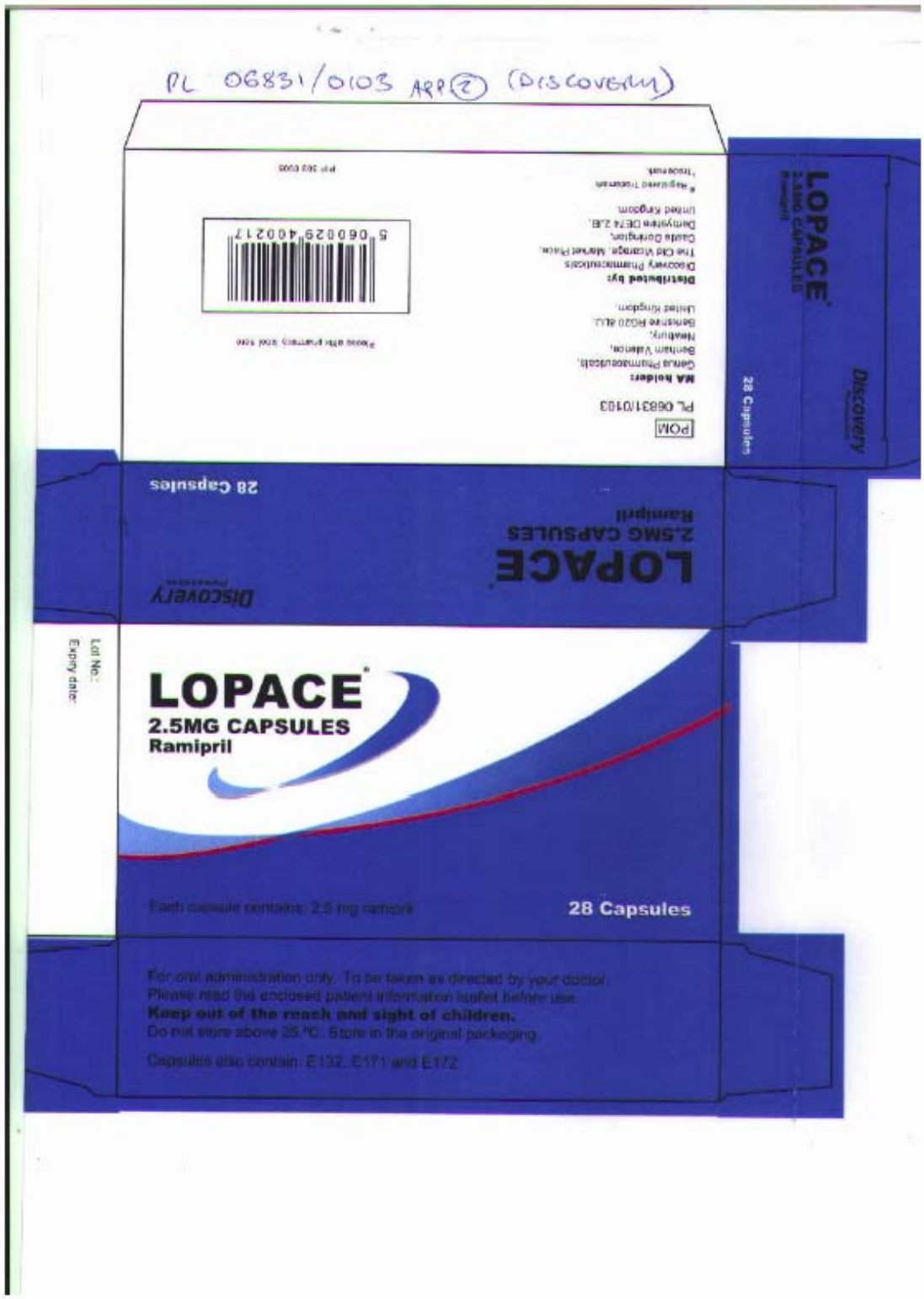
Discovery

# Module 4

# Labelling

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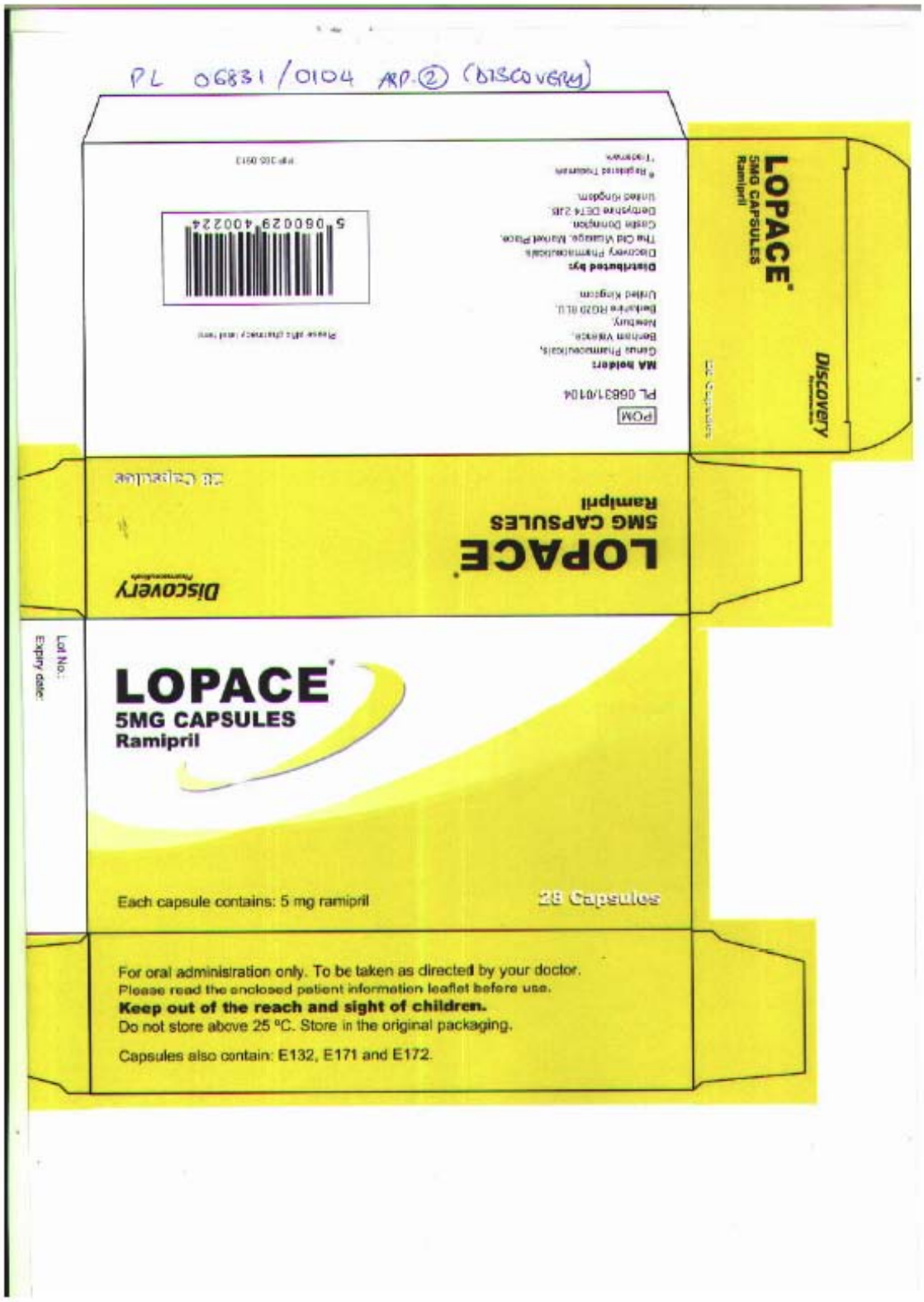
LOPACE
2.5MG CAPSULES
Ramipril
28 Capsules
Discovery
PL 06831/0103
POM
LOPACE
2.5MG CAPSULES
Ramipril
28 Capsules
Discovery
Lot No.:
Expiry date:
LOPACE
2.5MG CAPSULES
Ramipril
Each capsule contains: 2.5 mg ramipril
28 Capsules
For oral administration only. To be taken as directed by your doctor.
Please read the enclosed patient information leaflet before use.
Keep out of the reach and sight of children.
Do not store above 25 °C. Store in the original packaging.
Capsules also contain: E132, E171 and E172


PL 06831/0104 ARP.② (DISCOVERY)
LOPACE
5MG CAPSULES
Ramipril
28 Capsules
Discovery
LOPACE
5MG CAPSULES
Ramipril
Lot No.:
Expiry date:
LOPACE
5MG CAPSULES
Ramipril
Each capsule contains: 5 mg ramipril
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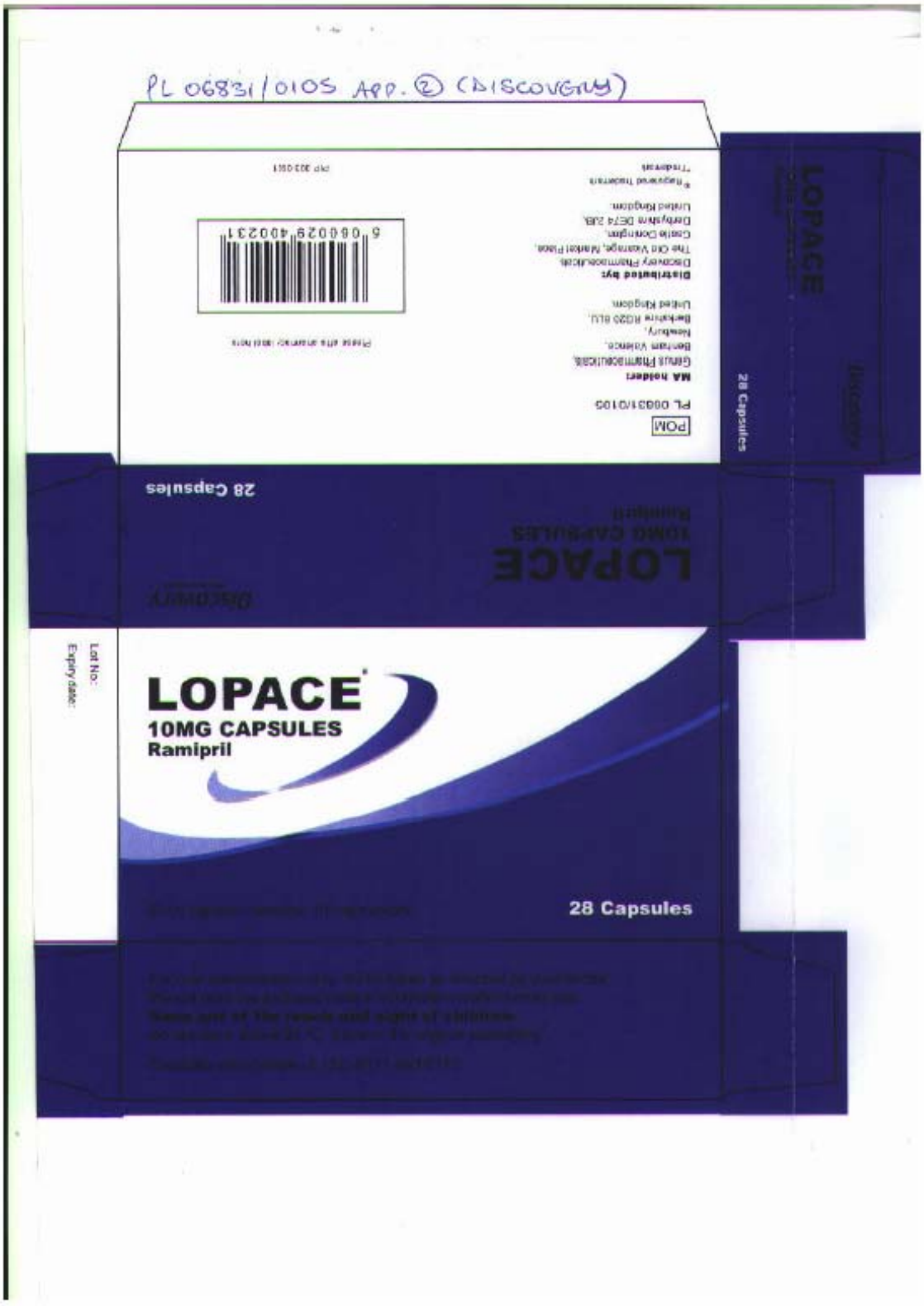
Capsules also contain: E132, E171 and E172.


PL 06831/0105 App. ② (DISCOVERY)
LOPACE
10MG CAPSULES
Ramipril
28 Capsules
Lot No:
Expiry date:
PL 00031/0105
POM
28 Capsules

# Module 5

# Scientific discussion during initial procedure

## 1. INTRODUCTION

### Background

These applications were submitted by Genus Pharmaceuticals Limited for generic versions of ramipril, via the Mutual Recognition Procedure. The originator product is Tritace capsules licensed to Aventis Pharma - UK) on 28th November 1989.

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Ramipril Capsules could be approved for the following 3indications:

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

Marketing Authorisations were granted in Austria, Belgium, Czech Republic, Hungary, Ireland, Luxembourg, and Slovakia. The product names in these CMS's are:

| | |
|---|---|
| **Austria:** | Ramipril Stada xxmg Kapseln |
| **Belgium:** | Ramipril EG xxmg Capsules |
| **Czech Republic:** | RAMICARD |
| **Hungary:** | RAMICARD |
| **Ireland** | Ramatan xxmg Capsules |
| **Luxembourg:** | Ramipril EG xxmg Capsules |
| **Slovakia:** | RAMICARD |

**Overall Benefit/Risk Assessment**

No new preclinical or clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

# 2. QUALITY ASPECTS

## INTRODUCTION

These abridged applications are for immediate-release capsules containing 1.25mg, 2.5 mg, 5 mg and 10 mg ramipril which are claimed to be essentially similar and cross refer to Tritace® 1.25mg, 2.5 mg, 5 mg and 10 mg capsules (PL 13402/0021-4) the UK brand leaders marketed by Hoechst Marion Roussel Limited (trading as Aventis Pharma). Tritace 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules were first authorised in the UK on 28th November 1989. Thus the 10-year period of exclusivity rule is satisfied.

The capsules are intended for reducing the risk myocardial infarction (MI), 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 (coronary artery bypass graft) or multivessel PTCA (percutaneous transluminal coronary angioplasty)), stroke or peripheral vascular disease. They are also indicated for reducing the risk of MI, 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 > 160 mmHg or diastolic blood pressure > 90 mmHg); high total cholesterol (> 5.2 mmol/L); low HDL (< 0.9 mmol/L); current smoker; known microalbuminuria; clinical evidence of previous vascular disease. Additionally, the capsules are indicated for the treatment of mild to moderate hypertension and congestive heart failure as adjunctive therapy to diuretics with or without cardiac glycosides.

There is no paediatric development programme associated with these products.

## DRUG SUBSTANCE

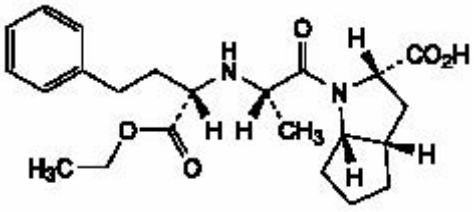
### General information

The drug substance is sourced from two suppliers. For these applications, an appropriate letters of access has been provided by both suppliers.

### Nomenclature

Ramipril Ph. Eur. is (2*S*,3a*S*,6a*S*)-1-[(S)-2-[[(*S)* -1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]-octahydro cyclopenta[*b*]pyrrole-2-carboxylic acid. Its molecular formula is $C_{23}H_{32}N_2O_5$ and the relative molecular mass is 416.5**.**
The CAS number for ramipril is 87333-19-5.

### Structure



**General properties**

A white or almost white, crystalline powder, sparingly soluble in water, freely soluble in methanol. Ramipril does not exhibit polymorphism and is not hygroscopic.

**Specification**

The drug substance specifications from both suppliers comply with the Ph. Eur. specification with additional tests for residual solvents.

**DRUG PRODUCT**

**Description and composition of the Drug Product:**

Ramipril capsules: 1.25mg, 2.5mg, 5mg and 10mg are capsules containing white or almost white powder which is a mixture of the active substance (Ramipril Ph Eur) and pre-gelatinised starch LM (Low Moisture). The capsules are differentiated by the colour of the shell, according to the strength of the capsules as demonstrated in the following table.

Appearance of finished product

| | **1.25mg** | **2.50mg** | **5.0mg** | **10.0mg** |
|---|---|---|---|---|
| Shape | Capsule | Capsule | Capsule | Capsule |
| Colour | Body Light Grey (L920)<br>Cap Light Grey (L920) | Body Light Grey (L920)<br>Cap Light Green (L720) | Body Light Grey (L920)<br>Cap Green (L730) | Body Light Grey (L920)<br>Cap Dark Green (L740) |
| Size | No 4 | No 4 | No 4 | No 4 |
| Markings | R on the cap and 1.25 on the body | R on the cap and 2.5 on the body | R on the cap and 5 on the body | R on the cap and 10 on the body |

The formulations are tabulated below:

| **Name of Constituents** | **Function** | **Reference to Standard** |
|---|---|---|
| Active constituent | | |
| Ramipril | Active | Ph Eur |
| Other Constituents | | |
| Starch, pregelatinised LM* | Filler | Ph Eur |

| | | |
|---|---|---|
| Body<br>- Gelatin pharmaceutical grade<br>- Water<br>- Black iron oxide (E172)<br>- Titanium dioxide (E171) | Structurant<br><br><br>Colorant<br>Colorant | Ph Eur<br><br><br>NF<br>Ph Eur |
| - Gelatin pharmaceutical grade<br>- Water<br>- Black iron oxide (E172)**<br>- Titanium dioxide (E171)<br>- Indigo carmine FD&C Blue 2 (E132)***<br>- Yellow iron oxide (E172)*** | Structurant<br><br><br>Colorant<br>Colorant<br>Colorant<br><br>Colorant | Ph Eur<br><br><br>NF<br>Ph Eur<br>NF<br>NF |

* Low Moisture
** 1.25mg & 10mg strengths only
*** 2.5mg, 5mg & 10mg strengths only

The capsules are either blister packed (Al/Al) or packed in polypropylene bottles with Snap-On polyethylene closures. A desiccant is inserted in each bottle.

**Clinical Trial Formula**

The clinical trial formula was the same as the marketing formula, but the colour of the capsules were different from those proposed for marketing. Ramipril 10mg capsules used for Bio-equivalence studies were dark green (L740)/dark green (L740) instead of being light grey (L920)/dark green (L740). It is stated that the difference in the colour is not important; as it has no influence on the dissolution tests carried out using different colour capsules. This is acceptable.

**Pharmaceutical Development**

The aim of the project was to develop a generic product, Ramipril Capsules, which is essentially similar to the originator product (Tritace by Aventis Pharma, UK)

The formulations of the generic products are similar to that of the originator products. The generic products contain the active substance ramipril and the excipient starch pregelatinised "low moisture" while the originator products have starch pregelatinised. The originator products use erythrosine as a colorant in the capsule shell's formulation, but the generic products do not have this colorant. The other colorants used in the generic products capsule shell, such as Titanium dioxide (E171), indigo carmine (E132) and Iron oxide (E172) are present in the originator products as well. Both products are presented in gelatin capsules.

**Formulation Development**

The analytical results given for the scale-up batches, which were subjected to full tests and checks according to the finished product specifications and limits, are acceptable and comply with the proposed specifications.

*In-Vitro* Dissolution Testing

The dissolution behaviour of the scale-up batches was compared with that of comparator products obtained from the UK and Dutch markets (Tritace capsules) and from French and Nordic markets (Denmark, Norway and Sweden) (Triatec capsules). The Tritace capsules from the UK market were manufactured by Aventis Pharma UK.

The procedure used for dissolution tests was that of the Ph Eur and similar dissolution profiles are evident.

Bioavailability

One bioequivalence study has been conducted between ramipril 10mg capsules, (Actavis HF) and Tritace 10mg (ramipril) capsules Aventis Pharma UK.
Both test and reference batches, were analysed fully by the finished product manufacturer and the certificates of analysis were provided. The bioequivalence study used a batch which was a production scale batch but the colour of the capsules was not the one proposed for marketing and as discussed before this has no influence over bioavailability.

The bioequivalence study was an open label single dose, randomised, two-way crossover relative study carried out in 38 healthy male and female volunteers.

Each study phase lasted 120 hours and the subjects were under clinical observations during the first 24 hours of the study.

Blood samples were drawn at 0.167; 0.33; 0.5; 0.75; 1.0; 1.5; 2; 2.5; 3.0; 3.5; 4.0; 5.0; 7.0; 11.0; 16; 24; 48; 72; 96 and 120 hours after the administration of the drugs.

The samples were processed and analysed using a validated HPLC method coupled with mass spectrometer to detect and quantitate the samples. The method used quinapril and quinaprilat as internal standards for analysing ramipril and ramiprilat respectively.
Using samples of human serum spiked with ramipril and ramiprilat; the HPLC method was validated for:
Specificity; Sensitivity; Between-Batch precision and accuracy; Within-Batch precision and accuracy; Linearity; Dilution integrity and Stability of the sample (including long term stability, bench top stability, freeze and thaw stability and stock solution stability). This is acceptable.
Area under the curve ($AUC_{last}$ and $AUC_{inf}$), $C_{max}$, $t_{max}$ and $t_{½}$ were studied both for ramipril and its metabolite ramiprilat.
For all of the above mentioned parameters the least square mean for ramipril (Actavis HF

and Tritace) and for ramiprilat (Actavis HF and Tritace) are tabulated, and all show comparable results. The ratios of least square means (test/reference) (%) are provided together with 90% confidence interval of the ratio (%).

**Summary of Pharmacokinetic Parameters Obtained For Ramipril (N = 36)**

| | **Least square mean Ramipril 10mg (D) Test** | **Least square mean Tritace (reference)** | **Ratio of least square means test/reference (%)** | **90% Confidence Interval of ratio(%)** |
|---|---|---|---|---|
| ln $AUC_{last}$hx (ng/ml) | 16.4 | 16.6 | 98.5 | 91.3 – 106.3 |
| ln $AUC_{inf}$ hx (ng/ml) | 17.0 | 17.0 | 100.3 | 91.4 – 109.9 |
| ln $C_{max}$ (ng/ml) | 21.7 | 21.4 | 101.4 | 84.9 – 121.1 |
| $t_{max}$ (hours) | 0.60 | 0.66 | | |
| $t_{½}$ (hours) | 1.5 | 1.6 | | |

**Summary of Pharmacokinetic Parameters Obtained For Ramiprilat (N = 36)**

| | **Least square mean Ramipril 10mg (D) Test** | **Least square mean Tritace (reference)** | **Ratio of least square means test/reference (%)** | **90% Confidence Interval of ratio(%)** |
|---|---|---|---|---|
| ln $AUC_{last}$hx (ng/ml) | 230.3 | 229.1 | 100.5 | 96.7 – 104.5 |
| ln $AUC_{inf}$ hx (ng/ml) | 293.3 | 294.2 | 99.7 | 95.8 – 103.7 |
| ln $C_{max}$ (ng/ml) | 21.5 | 20.5 | 104.8 | 95.9 – 114.5 |
| $t_{max}$ (hours) | 2.3 | 2.4 | | |
| $t_{½}$ (hours) | 78.8 | 79.6 | | |

From the data shown in the tables and from the near superimposable graphs of mean plasma, ramipril and ramiprilat concentrations it can be concluded that Ramipril 10mg Actavis HF and Tritace 10 mg Aventis Pharma UK are bioequivalent.

There was no bioequivalence study for other strengths of the product. However the results of dissolution tests indicate that the other strengths of Ramipril have similar

dissolution behaviour to comparator products and capsules of different strength have a very similar formulation. Extrapolation of the results of the bioequivalence study with the 10 mg product to other strengths is acceptable considering their relative compositions, methods of manufacture, dissolution profiles and pharmacokinetics over the dose range.

Impurity Profile

A comparative study of the impurities in the Ramipril capsules 1.25 mg and 10 mg and the originator product Tritace 1.25 mg and 10 mg has been performed. Based on these results, limits have been proposed for impurities at the time of release and at the end of the shelf life.

Essential Similarity

The comparative dissolution tests, the bioequivalence study and the impurity profile tests were designed and executed to establish the essential similarity between the originator products and the generic ramipril capsules. Taking the results all together the essential similarity is established.

TSE

Gelatin is the only substance derived from animal sources and is present in Ramipril capsule. Copies of TSE Certificates of Suitability for gelatin from the supplier of the capsules are provided.

**Manufacture**

A standard process of mixing, sieving and filling is used in the manufacture of these capsules.

**In-Process Controls**

Suitable in-process controls are performed.

**Validation of Manufacturing Process**

Validation was carried out according to the process validation report VAL 2141.

The applicant has provided a post-authorisation validation protocol. Two lots of each strength will be manufactured and both sources of drug substance will be used to manufacture each strength.

The applicant has provided an assurance that the specification to which the finished capsules are tested will be in accordance with the approved finished product specification.

**Control of Excipients**

Specifications for the excipients used

| Ingredients | Specifications |
|---|---|
| Starch pre-gelatinised LM* | Ph. Eur |
| Gelatin capsules ingredients | |
| Gelatin pharmaceutical grade | Ph. Eur |
| Water | |
| Black iron oxide (E172) | NF |
| Titanium dioxide (E171) | Ph. Eur |
| Indigo Carmine FD&C Blue 2 (E132) | NF |
| Yellow iron oxide (E172) | NF |

*Low moisture

Copies of relevant monographs from the Ph Eur were supplied. Low moisture grade (79%) pregelatinised starch is specified in order to minimise hydrolytic degradation of ramipril on storage.

There are no tests procedures for gelatin and titanium dioxide in the dossier as these are the ingredients of the capsule. The tests performed on the capsules when received, will be described later. Certificates of analysis for pre-gelatinised starch from the supplier and finished product manufacturer were provided. These tests are according to the Ph Eur. This is acceptable.

The capsules used are size 4 hard gelatin capsules with different colours for the body and the cap.

It is stated that titanium dioxide, iron oxides (yellow and black), indigo carmine FD & C Blue 2 comply with the EEC Commission's Directive 95/45/EC of 1995 which gives specific purity criteria concerning colours for use in food stuff. This is acceptable.

Most of the analytical procedures used for testing the excipients and the specifications for them are based on the specific monographs given in the Ph Eur.

The gelatin used in the capsules is of animal origin and the copies of TSE certificates of suitability are provided. This is acceptable.

## Control of Drug Product

### Specifications

The specifications for the release of the manufactured products are similar to those at the end of shelf life. Most of the specifications comply with the relevant Ph Eur general monographs and the test procedures are validated (see the validation of analytical procedures).

### Analytical Procedures

Details of the analytical methods used have been supplied and are acceptable.

### Validation Methods

Full validation details were provided and are acceptable.

### Batch Analysis

Analytical results were supplied for several batches of each strength. Certificates of analyses (CoA) for these batches are provided. All results comply with the specifications.

### Characterisation of Impurities

The impurities present in the products are characterised and the significant degradation products have been identified.

### Justification of Specification

The specification contains appropriate tests for control of the proposed dosage form. Degradation of ramipril is evident on storage. Specifications for assay have been tightened at batch release in order to ensure that batches will comply with end of shelf life specification. The latter has been justified in relation to stability data.

### Reference Materials

Certificates of analysis are provided in the dossier for the reference standard and demonstrate its suitability.

Certificates of analysis have been provided for the reference standards for all named impurities.

### Container Closure System

Ramipril capsules are packed in blister packs (Al/Al).

**Stability**

The stability batches have been packed into proposed blister packaging under the following storage conditions compliant with CHMP recommendations.

The analytical tests employed for the stability studies are the same as those described in the finished product specification.

**Stability Summary and Conclusion**

Two batches of each strength are included in the studies and were tested in accordance with the specifications although not all tests have been conducted at all time points. Batches were packed into both proposed marketing containers.

It is evident from the data that the 1.25mg capsules are less stable than the other formulations
Considering all of the data, widened shelf-life limits for assay and impurity D in the specification for 1.25mg capsules were agreed during national assessment. Wider assay limits were also agreed for the 2.5mg capsules at end of shelf life, based on data submitted during assessment.

The approved limits do not represent a concern in relation to safety or efficacy. Proposed shelf-lives are 18 months (1.25mg) and 24 months (2.5mg, 5mg, 10mg) with storage direction 'Do not store above 25$^{o}$C.
No significant pack effect is evident.

The applicant has committed to enter the first 3 production batches into stability studies across the range of strengths. Any out of specification results of significance will be reported to the Licensing Authority.

**ASSESSOR'S COMMENTS ON THE SPC**

Pharmaceutically acceptable

**COMMENT ON EXPERT REPORT**

The Quality Overall Summary is an adequate summary of the dossier.

## 3. NON-CLINICAL ASPECTS

These applications for a generic product claim essential similarity to Tritace® 1.25mg, 2.5 mg, 5 mg and 10 mg capsules (PL 13402/0021-4) the UK brand leaders marketed by Hoechst Marion Roussel Limited (trading as Aventis Pharma), which has been licensed within the EEA for over 10 years.

No new preclinical data has been supplied with these applications, however, a preclinical expert report summarising relevant non-clinical studies has been included in the MR dossier; this is satisfactory.

# 4. CLINICAL ASPECTS

## INTRODUCTION

This is a generic application for ramipril made under article 10.1(a)(iii), first paragraph. Essential similarity has been claimed with Tritace (Aventis Pharma).

## BACKGROUND

ACE inhibitors exhibit their pharmacological effects by inhibiting the formation of Angiotensin II, which has strong vasoconstrictive effects. They have been used as antihypertensives and when given early, also to reduce mortality and cardiovascular morbidity in patients with myocardial infarction.
Ramipril is a long acting ACE inhibitor, is a prodrug and forms active metabolite ramiprilat. The safety of efficacy of ramipril in various indications has been established.

## 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 is indicated for the treatment of mild to moderate hypertension.*

## DOSE & DOSE SCHEDULE

*Dosage and 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.*

*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.*

*Oral administration.*

# TOXICOLOGY

The toxicological profile of ramipril is very well known. A Non-Clinical Overall Summary has been written and the expert concludes that in common with other ACE inhibitors and given its potency as a therapeutic agent, ramipril shows a remarkable lack of toxicity after acute overdosage.

# CLINICAL PHARMACOLOGY

ATC code: C09A A05
Ramipril is a prodrug, which is hydrolysed in the liver to form the active angiotensin converting enzyme inhibitor ramiprilat.
The kinetic profile of ramipril is known as it has already been authorised and in clinical use for many years. The applicant has carried out limited kinetic study to investigate bioequivalence of the product compared with the reference product (Tritace, Aventis pharma).

## BIOEQUIVALENCE

The bioequivalence of ramipril 10mg capsules was compared with Aventis (Tritace 10mg capsules) in a randomised, comparative, open-label, single-dose, 2-way, cross-over study. A total of 38 healthy volunteers were recruited in the study and 36 analysed. The washout period was 21 days and products were administered under fasting conditions.

The results and kinetic profile for the parent compound as well as active metabolite are shown in the table below.

**Ramipril**

| | **Least squires mean** | **Least squares mean** | **Ratio of least squares means** | **90% CI** |
|---|---|---|---|---|
| | **Reference (Aventis)** | | | |
| In $AUC_{0-*4}$ (ng.h/ml) | 17.84 | 18.11 | 98.5% | 91.3 – 106.3% |
| In $AUC_{0-*inf}$ | 18.52 | 18.47 | 100.3% | 91.4 – 109.9% |

| | | | | |
|---|---|---|---|---|
| (ng.h./ml) | | | | |
| Ln Cmax* (ng/ml) | 23.66 | 23.34 | 101.4% | 84.9 – 121.1% |
| Tmax (h) | 0.595 | 0.659 | | |

**Ramiprilat**

| | **Least squares mean** | **Least square mean** | **Ratio of least square means** | **90% CI** |
|---|---|---|---|---|
| | **Reference (Aventis)** | | | |
| In $AUC_{0-4}$* (ng.h/ml) | 230.34 | 229.13 | 100.5% | 96.7 – 104.5% |
| In $AUC_{0-inf}$* (ng.h/ml) | 293.26 | 294.19 | 99.7% | 95.8 – 103.7% |
| Ln Cmax* (ng/ml) | 21.467 | 20.484 | 104.8% | 95.9 – 114.5% |
| Tmax (h) | 2.32 | 2.44 | | |

The Cmax and AUC ranges for the parent compound as well as active metabolites were within acceptable range. The bioequivalence of the product has been shown.

## EFFICACY

Efficacy of ramipril is known through its clinical use over many years and extensive publications. The clinical expert report has addressed the various indications for this product. No new data has been submitted and none is required.

## SAFETY

The clinical safety of the product is well established. No new data has been submitted and none is required.

## EXPERT REPORT

The clinical expert report was written by a Fellow of the Royal College of Physicians of London and a Medical Consultant.

## SUMMARY OF PRODUCT CHARACTERISTICS

The summary of product characteristics is identical to the SPC of the reference product.

## DISCUSSION

The clinical use of ramipril is well established in the indications proposed. The bioequivalence of the generic formulation has been shown against the reference product (Tritace from Aventis Pharma). The SPC is generally identical to the SPC of the reference product.

## CONCLUSIONS

Marketing authorisations have been granted for these products.

# 5. OVERALL CONCLUSION

## QUALITY

The important quality characteristics of Ramipril 1.25mg, 2.5mg, 5mg and 10mg capsules are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

## PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

## EFFICACY

Bioequivalence has been demonstrated between the applicant's Ramipril 10mg capsules and Tritace 10mg capsules. Given that similar dissolution results have been shown for all strengths and a similar formulation has been used, a separate bioequivalence study using the other strength capsules is not considered necessary.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

## RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with ramipril is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

# Module 6

## STEPS TAKEN AFTER AUTHORISATION - SUMMARY

| Date submitted | Application type | Scope | Outcome |
|---|---|---|---|
| | | | |
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