1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

RAMPIL 1,25 mg hard gelatin capsules

RAMPIL 2,5 mg hard gelatin capsules

RAMPIL 5 mg hard gelatin capsules

RAMPIL 10 mg hard gelatin capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule of RAMPIL 1,25 mg contains 1,25 mg of ramipril.

Each hard gelatin capsule of RAMPIL 2,5 mg contains 2,5 mg of ramipril.

Each hard gelatin capsule of RAMPIL 5 mg contains 5 mg of ramipril.

Each hard gelatin capsule of RAMPIL 10 mg contains 10 mg of ramipril.

Sugar free.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard gelatin capsules.

RAMPIL 1,25 mg is a hard gelatin size #4 capsule with yellow opaque body and yellow opaque cap. The cap has radially imprinted “RM 1,25”. Capsules contain a white to off-white powder.

RAMPIL 2,5 mg is a hard gelatin size #4 capsule with orange opaque body and orange opaque cap. The cap has radially imprinted “RM 2,5”. Capsules contain a white to off-white powder.

RAMPIL 5 mg is a hard gelatin size #4 capsule with Swedish orange opaque body and Swedish orange opaque cap. The cap has radially imprinted “RM 5”. Capsules contain a white to off-white powder.

RAMPIL 10 mg is a hard gelatin size #4 capsule with blue opaque body and blue opaque cap. The cap has radially imprinted “RM 10”. Capsules contain a white to off-white powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

RAMPIL is indicated for the following:

- Mild to moderate hypertension.
- Cardiac failure following myocardial infarction.
- To reduce proteinuria and the decline in glomerular filtration rate in patients with diabetic nephropathy and hypertension.

- To reduce the risk of myocardial infarction, stroke or cardiovascular death and to reduce the need for revascularisation procedures in patients with an increased cardiovascular risk such as manifest coronary heart disease (with or without a history of myocardial infarction), a history of stroke or a history of peripheral vascular disease.
- To reduce the risk of myocardial infarction, stroke or cardiovascular death in diabetic patients.

4.2. Posology and method of administration

Posology

Adults

Hypertension:

Initial dose is 2,5 mg RAMPIL once daily (for patients not on diuretics). The dose should be adjusted according to blood pressure response. Dosage should be increased to 5 mg RAMPIL and up to a maximum of 10 mg once daily at intervals of 1 to 2 weeks. The therapeutic dose range is 2,5 mg to 10 mg.

The full therapeutic effect may take several weeks. Therefore, if the desired effect has not been achieved within 2 to 4 weeks the dose may be increased.

To reduce the risk of myocardial infarction, stroke or cardiovascular death

Initial dose is 2,5 mg RAMPIL once daily. This may be increased at intervals of 4 weeks until the therapeutic effect is reached. Adjustments should be based on clinical response. The increase should be implemented by doubling the dose after one week of treatment. Three weeks later, it should be doubled again to the normal maintenance dose of 10 mg once daily.

Non-diabetic and diabetic nephropathy

Initial dose is 1,25 mg RAMPIL once daily. Adjustments should be based on clinical response. The dose, if increased, should be implemented by doubling the dose at intervals of two to three weeks. The maximum permitted daily dose is 10 mg.

Post-myocardial infarction

Treatment with RAMPIL should be initiated in hospital three to ten days after acute myocardial infarction if the patient manifests with evidence of heart failure and is haemodynamically stable.

2,5 mg twice daily for two days. If well tolerated the dose may be increased to 5 mg RAMPIL twice daily.

If patients are unable to tolerate 2,5 mg initially, 1,25 mg RAMPIL twice daily may be given initially and later increased to 2,5 mg twice daily.

Dosing in high-risk individuals

Diuretic-treated patients:

In order to minimise the possibility of sudden and severe hypotension which may occur within the first 1 to 5 hours after the initial dose of RAMPIL, diuretics should be discontinued 2 to 3 days before beginning therapy with RAMPIL. In patients where diuretic therapy cannot be discontinued, treatment with RAMPIL should be initiated with a 1,25 mg once daily dose. Subsequent dosage adjustments will depend on the therapeutic response.

Renovascular hypertension:

Dose should be lowered and the patient should be monitored.

Special populations

Renal impairment

RAMPIL is not recommended for use in dialysis patients

Paediatric population

The safety and efficacy of RAMPIL in children has not been established.

Method of administration

For oral administration

May be taken with/without meals preferably at the same time every day.

4.3. Contraindications

RAMPIL is contraindicated in:

- Patients with hypersensitivity to ramipril or to any excipients in RAMPIL (see section 6.1).
- Patients with a history of angioedema related to previous ACE- inhibitor therapy or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Aortic stenosis.
- Hypertrophic obstructive cardiomyopathy.
- Severe renal function impairment (creatinine clearance below 30 ml/min).
- Renal artery stenosis in patients with a single kidney.
- Bilateral renal artery stenosis.
- Concomitant therapy with potassium-sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.
- Lithium therapy: Concomitant administration with RAMPIL may lead to toxic blood concentrations of lithium (see section 4.5).

- Concomitant use with aliskiren-containing medicines (see section 4.4 and 4.5)
- Concomitant use of fluoroquinolones with ACE inhibitors/Angiotensin receptor blockers in patients with moderate to severe renal impairment and in elderly patients (see section 4.4 and 4.5).
- Pregnancy and lactation: teratogenicity has been shown in animals. Hypertensive women receiving ACE-inhibitors should take care to ensure that they do not become pregnant while taking an ACE-inhibitor. ACE-inhibitors pass through the placenta and can be presumed to cause disturbances in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in newborns have been reported after administration of ACE-inhibitors in the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.4 and 4.6).
- RAMPIL is not recommended for use in children.
- Concomitant use with sacubitril/valsartan therapy is contraindicated
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces

4.4. Special warnings and precautions for use

Should a woman become pregnant while receiving RAMPIL, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine. Should a woman contemplate pregnancy, the doctor should consider an alternative medicine (see section 4.3 and 4.6).

Hypersensitivity/ angioedema

Angioedema has been reported in patients treated with ACE inhibitors including RAMPIL.

If angioedema of the face, extremities, lips, tongue, glottis and/or larynx is observed in patients treated with RAMPIL, RAMPIL should be discontinued promptly. These patients should be monitored to ensure complete resolution of symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is oedematous involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate emergency therapy should be administered. This may include the administration of epinephrine (adrenaline) and/or the maintenance of a patent airway. The patient should be kept under close medical supervision for at least 12 to 24 hours and discharged after complete and sustained resolution of symptoms has occurred. These patients should never receive RAMPIL or any other ACE inhibitor or ARB again.

This risk of angioedema may be increased in patients taking concomitant medicines which may cause angioedema such as mTOR (mammalian target of rapamycin) inhibitors (e.g. temsirolimus, everolimus, sirolimus), vildagliptin or neprilysin (NEP) inhibitors (such as racecadotril). The combination of ramipril as in RAMPIL, with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.5).

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

Anaphylactoid reactions

Anaphylactoid reactions have occurred in patients using ACE inhibitors during desensitising protocols involving for example, hymenoptera venom. The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom and other allergens are increased under ACE inhibition. A temporary discontinuation of RAMPIL should be considered prior to desensitization.

Anaphylactoid reactions have been reported in patients exposed to either high-flux membrane dialysis or low-density lipoprotein apheresis with dextran sulfate absorption.

Ethnic differences

RAMPIL causes a higher rate of angioedema in black patients than in non-black patients. Ramipril as in RAMPIL 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.

Cerebrovascular disease or ischaemic heart disease

Reduction in blood pressure could aggravate these conditions and may result in myocardial infarction and cerebrovascular accidents.

Volume depleted patients (e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting)

Although it may occur in normovolemic patients, hypotension is more likely in volume depleted patients. A sudden reduction in angiotensin II may result in sudden and severe hypotension. There is also an increased risk of RAMPIL-induced renal failure, especially in those with congestive heart failure.

Patients at a high risk of symptomatic hypotension e.g. patients with salt or volume depletion with or without hyponatraemia should have these conditions corrected before commencing therapy with RAMPIL. Monitoring is required after initiating therapy. If hypotension occurs, the patient should be placed in the supine position and if necessary, receive an intravenous infusion of 0,9 % saline.

Severe autoimmune disease, especially systemic lupus erythematosus, other collagen vascular diseases or scleroderma

Increases the risk for development of neutropenia or agranulocytosis.

Neutropenia, agranulocytosis, as well as thrombocytopenia and anaemia, have been 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 leucopoenia. 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 medicines that can cause changes in the blood picture.

Acute myocardial infarction

In acute myocardial infarction, treatment with RAMPIL should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentrations exceeding 177 micromol/L or proteinuria exceeding 500 mg/24 hours). If renal dysfunction develops during treatment (serum creatinine concentrations exceeding 177 micromol/L or doubling of the pre-treatment value) then RAMPIL may need to be withdrawn (see section 4.3).
In acute myocardial infarction, patients may develop persistent hypotension and/or impaired renal function.

Hypotension in acute myocardial infarction

Treatment with RAMPIL must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These include patients with systolic blood pressure of 100 mmHg or lower, or cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mmHg or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2,5 mg if systolic blood pressure is 100 mmHg or lower. If hypotension persists (systolic blood pressure less than 90 mmHg for more than 1 hour) then RAMPIL should be withdrawn.

Diabetes mellitus

Increased risk of hyperkalaemia, as well as hypoglycaemia may occur.

Renovascular disease

RAMPIL should not be used in patients with renovascular disease or suspected renovascular disease but it may be used cautiously in severe resistant hypertension in such patients. In this instance RAMPIL should only be used under specialist supervision. The elderly, patients with peripheral vascular diseases or generalised atherosclerosis may have asymptomatic renovascular disease (see section 4.2).

Renal artery stenosis, bilateral or in one kidney, or renal transplant

Increased risk of renal function impairment may increase blood urea and serum creatinine concentrations, which may be reversible upon discontinuation of therapy. There is also an increased risk of agranulocytosis and neutropenia when immunosuppressants are concurrently administered.

Renal function impairment

In renal function impairment, decreased elimination of RAMPIL will result in an increased risk of hyperkalaemia. These patients may require lower doses.

Monitoring of renal function

Renal function should be assessed before and during treatment and dose adjusted especially in the initial weeks of treatment. Careful monitoring is required in patients with renal impairment. There is a risk of impairment of renal function, particularly in patients with congestive heart failure or after a renal transplant.

Surgery

In patients undergoing major surgery or during anaesthesia with medicines that produce hypotension, RAMPIL may block angiotensin II formation secondary to complementary renin release. If hypotension occurs and is due to this mechanism, it can be corrected by volume expansion.

Impaired liver function

In patients with impaired liver function, the metabolism of the parent compound ramipril, as in RAMPIL, and therefore the formation of the bioactive metabolite ramiprilat is decelerated resulting in markedly elevated plasma ramipril levels due to a diminished activity of esterases in the liver. Use of RAMPIL in patients with impaired liver function is not recommended.

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 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 medicines that produce hypotension.

Dual blockade of the renin-angiotensin-aldosterone system

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of RAMPIL and aliskiren is therefore contraindicated (see section 4.3 and 4.5).

Electrolyte Monitoring: Hyperkalemia

RAMPIL may cause an increase in serum potassium levels.

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

Electrolyte Monitoring: Hyponatremia

Syndrome of Inappropriate Anti-diuretic Hormone (SIADH) and subsequent hyponatremia has been observed in some patients treated with ramipril, as in RAMPIL. It is recommended that serum sodium levels be monitored regularly in the elderly and in other patients at risk of hyponatremia.

Blood urea and serum creatinine

Increases in blood urea and serum creatinine may occur in patients with no apparent pre-existing vascular disease, especially when RAMPIL has been given concomitantly with a diuretic. Dosage reduction or discontinuation of RAMPIL or the diuretic may be required.

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.

Fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers

Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolones or ACE inhibitors/Angiotensin receptor blockers whether used separately and/or concomitantly (see section 4.3 and 4.5).

The treatment of hypertension with RAMPIL must be carried out under regular medical supervision.

Paediatric population

The safety and efficacy of RAMPIL in children has not been established (see section 4.3).

4.5. Interaction with other medicines and other forms of interaction

Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see section 4,3 and 4.4).

Sacubitril/valsartan

The concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.4). Treatment with RAMPIL must not be started until 36 hours after taking the last dose of sacubitril/valsartan. Sacubitril/valsartan must not be started until 36 hours after the last dose of RAMPIL.

Neprilysin (NEP) inhibitors

An increased risk of angioedema has been reported for a concomitant use of ACE inhibitors and NEP inhibitor such as racecadotril.

Extracorporeal treatments

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. If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive medicines.

Antihypertensive medicines (e.g. diuretics) and other medicines that may decrease blood pressure (hypotension-producing medicines) (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.

The antihypertensive effect is additive. Dosage adjustments may be necessary during concurrent use or when one medicine is discontinued.

Loop thiazide or related diuretics

"First dose hypotension" may occur (see section 4.2). RAMPIL may attenuate potassium loss caused by thiazide-type diuretics. Therefore, if concomitant use of these medicines is indicated they should be given with caution and with frequent monitoring of serum potassium.

Nonsteroidal anti-inflammatory medicines (NSAIDs) e.g. indomethacin

It may reduce the antihypertensive effects of RAMPIL. Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with RAMPIL. 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.

Potassium supplements, heparin or other plasma potassium increasing active supplements or medicines e.g. Angiotensin II antagonists, trimethoprim and fixed dose combination with sulfamethoxazole, tacrolimus, ciclosporin

Concurrent administration may result in hyperkalaemia, therefore close monitoring of serum potassium is required.

Lithium

Increases in lithium concentrations have been reported (see section 4.3).

Vasopressor sympathomimetic and other medicines

If they reduce the antihypertensive effect of RAMPIL then blood pressure monitoring is recommended.

Allopurinol, cytostatic and immunosuppressive medicines, systemic corticosteroids, procainamide and other medicines that may change the blood cell count

Concomitant use with ACE inhibitors may lead to an increased risk for haematological reactions.

Antidiabetic medicines (insulin and oral medicines)

Hypoglycaemic reactions may occur. Blood glucose monitoring is recommended.

Fluoroquinolones

Concomitant use of fluoroquinolones and ACE inhibitors/ Angiotensin receptor blockers may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3)

mTOR inhibitors or DPP-IV inhibitors:

An increased risk of angioedema is possible in patients taking concomitant medicines such as mTOR inhibitors (e.g. temsirolimus, everolimus, sirolimus) or vildagliptin. Caution should be used when starting therapy.

4.6. Fertility, pregnancy and lactation

RAMPIL should not be used during pregnancy and breastfeeding (see section 4.3).

Pregnancy

The use of RAMPIL is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take RAMPIL during pregnancy (see section 4.3). 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 RAMPIL should be stopped immediately and if appropriate, alternative therapy should be started.

Foetal exposure to ACE inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spins bifida) and of kidney malformations.

RAMPIL passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in newborns, have been reported after administration of RAMPIL in the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur. In addition, use of RAMPIL during the first trimester of pregnancy has been associated with an increased risk of birth defects, in particular of the cardiovascular and the central nervous system (see section 4.3 and 4.4).

Breastfeeding

Safety in lactation has not been established.

Alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

Fertility

No data are available.

4.7. Effects on ability to drive and use machines

RAMPIL has minor influence on the ability to drive and or operate machinery.

Since adverse reactions such as dizziness and visual disturbances have been reported in patients receiving RAMPIL patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that RAMPIL does not adversely affect their ability to do so (see section 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

The safety profile of RAMPIL 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.

b) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders		Decreases in white blood cell count, haemoglobin and haematocrit, bone marrow depression, anaemia, thrombocytopenia, agranulocytosis, haemolytic anaemia, decreases in platelet count, eosinophilia	Elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis, bone marrow failure, pancytopenia,
Immune system disorders			Positive antinuclear antibodies (ANA), anaphylactic or anaphylactoid reactions

Endocrine disorders			Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Blood potassium increased (hyperkalaemia)	Hyponatraemia, increases in blood urea, increases in serum creatinine, anorexia, decreased appetite	
Psychiatric disorders		Depressed mood, anxiety, nervousness, restlessness, sleep disorders including somnolence, confusional state	Disturbance in attention
Nervous system disorders	Dizziness, headache	Paraesthesia, vertigo, ageusia, dysgeusia, tremor, balance disorder, cerebrovascular accident	Cerebral ischaemia including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired, burning sensation, parosmia
Eye disorders		Visual disturbance blurred vision, conjunctivitis	
Ear and labyrinth disorders		Hearing impaired, tinnitus	
Cardiac disorders		Myocardial ischaemia, including angina pectoris or myocardial infarction, palpitations, tachycardia, peripheral oedema, dysrhythmia	
Vascular disorders	Hypotension, decrease in orthostatic blood pressure, syncope	Flushing, vasculitis, vascular stenosis, hypoperfusion	Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Non-productive tickling cough, bronchitis, dyspnoea, sinusitis	Bronchospasm including aggravated asthma, rhinitis, nasal congestion	
Gastrointestinal disorders	Diarrhoea, nausea, gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, vomiting	Abdominal pain upper including gastritis, indigestion, dry mouth, pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), increased pancreatic enzymes small bowel angioedema, taste disturbances, constipation	Aphtous stomatitis
Hepatobiliary disorders		Hepatitis (hepatocellular or cholestatic), jaundice, increases in liver enzymes, increases in serum bilirubin	Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional).

Skin and subcutaneous tissue disorders	Rash (maculo-papular)	Urticaria, diaphoresis, alopecia, pruritus, psoriasis, severe skin disorders including pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme, photosensitivity reaction, hypersensitivity/angioedema reactions which may be fatal: angioedema of the face, lips, tongue, glottis and/or larynx, extremities and intestinal angioedema, hyperhidrosis exfoliative dermatitis, onycholysis,	Aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema,
Musculoskeletal and connective tissue disorders	Muscle spasms, myalgia	Arthralgia	
Renal and urinary disorders		Uraemia, oliguria, anuria, renal dysfunction, renal impairment including acute renal failure, urine output increased, worsening of a pre-existing proteinuria,	
Reproductive system and breast disorders		Transient erectile impotence, decrease in libido	Gynaecomastia
General disorders and administrative site conditions	Chest pain, fatigue	Pyrexia, asthenia	

c) *Description of selected adverse reactions*

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088/ +27 (0)11 239-6200

4.9. Overdose

See section 4.4 and 4.8.

Symptoms

Symptoms associated with overdosage of ACE inhibitors may include excessive peripheral vasodilatation (with marked severe hypotension, shock), bradycardia, electrolyte disturbances, and renal failure.

Treatment

The patient should be closely monitored. Treatment is symptomatic and supportive. Activated charcoal may be given in severe overdosage if the patient presents within 1 hour of ingestion. Treatment consists of volume expansion to correct hypotension and treating dehydration and electrolyte imbalances. RAMPIL is poorly removable by haemodialysis. Suggested measures include primary detoxification (administration of adsorbents) and measures to restore haemodynamic stability, including, administration of alpha 1 adrenergic agonists or angiotensin II (angiotensinamide) administration.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 7.1.3 Other hypotensives

Pharmacotherapeutic group: ACE Inhibitors, Plain

ATC code: C09AA05

Mechanism of action

Ramipril inhibits angiotensin I-converting enzyme (ACE) activity. It inhibits the conversion of the relatively inactive angiotensin I to the active angiotensin II. Angiotensin II is a potent vasoconstrictor and stimulates the release of aldosterone. Decreased angiotensin II levels result in a decrease in vasopressor activity and a reduction in aldosterone secretion, which may result in small increases in serum potassium.

It is also thought that ACE inhibition may inhibit degradation of bradykinin, leading to increased bradykinin levels.

5.2. Pharmacokinetic properties

Absorption

Following oral administration, ramipril is rapidly absorbed from the gastrointestinal tract, and peak plasma concentrations of ramipril are reached within one hour. The extent of absorption after oral administration is 60 % with wide variability between patients.

Food intake has no relevant influence on the extent of absorption.

Distribution

The plasma half-life is increased in renal impairment. The time to achieve peak serum concentration is within 1 hour.

The protein binding of ramipril is about 73 %.

Biotransformation

Ramipril is a prodrug, which is converted in the liver to its diacid metabolite, ramiprilat, by cleavage of an ester group.

Ramipril is almost completely metabolised and the metabolites are excreted mainly via the kidneys.

Elimination

Ramipril is renally eliminated and excreted 100 % unchanged in the urine.

With impaired renal function the elimination of ramipril from plasma is delayed and the urinary excretion reduced.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

RAMPIL 1,25 mg

Gelatin, iron oxide yellow (C.I. 77492), pregelatinised starch, titanium dioxide (C.I. 77891)

RAMPIL 2,5 mg

Erythrosine (C.I. 45430), gelatin, iron oxide yellow (C.I. 77492), pregelatinised starch, titanium dioxide (C.I. 77891)

RAMPIL 5 mg

Carmoisine (C.I. 14720), gelatin, pregelatinised starch, quinolone yellow (C.I. 47005), titanium dioxide (C.I. 77891)

RAMPIL 10 mg

Gelatin, indigotine (C.I. 73015), iron oxide black (C.I. 77499), ponceau 4R (C.I. 16255), pregelatinised starch, titanium dioxide (C.I. 77891)

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C in tightly closed containers.

Protect from light.

Keep the blisters in the carton until required for use.

6.5. Nature and contents of container

30 or 60 hard gelatin capsules are packed in a white, round, polypropylene securitainer with a white snap-on low-density polyethylene cap.

30 or 60 hard gelatin capsules are packed in clear polyvinylchloride/polyvinylidene chloride blister strips sealed with an aluminium foil backing. The blister strips containing 10 capsules are packed into an outer cardboard carton together with a leaflet.

30 or 60 hard gelatin capsules are packed in polyvinylchloride/ACLAR blister strips sealed with an aluminium foil backing. The blister strips containing 10 capsules are packed into an outer cardboard carton together with a leaflet.

30 or 60 hard gelatin capsules are packed in polyamide/aluminium/polyvinylchloride blister strips sealed with an aluminium foil backing. The blister strips containing 10 capsules are packed into an outer cardboard carton together with a leaflet.

Not all packs or pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBERS

RAMPIL 1,25 mg: A39/7.1.3/0141

RAMPIL 2,5 mg: A39/7.1.3/0142

RAMPIL 5 mg: A39/7.1.3/0143

RAMPIL 10 mg: A39/7.1.3/0144

9. DATE OF FIRST AUTHORISATION

25 November 2005

10. DATE OF REVISION OF TEXT

04 January 2023

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088.

Botswana: S3	
5 mg:	BOT1302411
10 mg:	BOT1302412

Namibia: NS2

1,25 mg:	10/7.1.3/0496
2,5 mg:	10/7.1.3/0497
5 mg:	10/7.1.3/0498
10 mg:	10/7.1.3/0499

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