**PACKAGE INSERT**

**SCHEDULING STATUS:** **S3**

**PROPRIETARY NAMES AND DOSAGE FORMS:**

RAMIPRIL HEXAL 2,5 (tablets)
RAMIPRIL HEXAL 5 (tablets)

**COMPOSITION:**

Each Ramipril Hexal 2,5 tablet contains 2,5 mg ramipril as active substance.
Each Ramipril Hexal 5 tablet contains 5 mg ramipril as active substance.

**PHARMACOLOGICAL CLASSIFICATION:**

A 7.1.3 Other hypotensives

**PHARMACOLOGICAL ACTION:**

RAMIPRIL HEXAL inhibits angiotensin 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. Ramipril is a prodrug, which is hydrolyzed in the liver after absorption from the gastrointestinal tract to form the active angiotensin converting enzyme inhibitor, ramiprilat. It is also thought that ACE inhibition may inhibit degradation of bradykinin, leading to increased bradykinin levels.

**Pharmacokinetics*:***
The extent of absorption after oral administration is estimated to be 30 to 60 % with wide variability between patients. The plasma half-life is 13 to 17 hours for ramiprilat for 5 to 10 mg ramipril doses, and several times longer for lower doses such as 1,25 to 2,5 mg, which is increased in renal impairment. The time to achieve peak serum concentration is within 1 hour and 2 to 4 hours for ramiprilat. Ramipril is renally eliminated and excreted 100 % unchanged in the urine.

**INDICATIONS:**

- 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.

**CONTRAINDICATIONS:**

- Sensitivity to any of the components of RAMIPRIL HEXAL.
- Patients with a history of angioedema related to previous ACE-inhibitor therapy or angiotension receptor blocker.
- 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.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride.
- Porphyria.

**WARNINGS AND SPECIAL PRECAUTIONS:**

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|---|
| Should a woman become pregnant while receiving an ACE inhibitor, the treatment must be stopped promptly and changed to a different medicine (see “PREGNANCY AND LACTATION”). If a woman is contemplating pregnancy, a different class of medicine should be used (see “PREGNANCY AND LACTATION”). |

RAMIPRIL HEXAL should be used with caution in the following conditions:

- 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 normo volumic 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 RAMIPRIL HEXAL 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 hyponatremia should have these conditions corrected before therapy with RAMIPRIL HEXAL. Monitoring is required after initiating therapy.
- Severe autoimmune disease, especially systemic lupus erythematosus, other collagen vascular disease or scleroderma: Increase the risk for development of neutropenia or agranulocytosis.
- In acute myocardial infarction, treatment with RAMIPRIL HEXAL should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentrations exceeding 177 µmol/ℓ or proteinuria exceeding 500 mg/24 hours). If renal dysfunction develops during treatment (serum creatinine concentrations exceeding 177 µmol/ℓ or doubling of the pretreatment value) then RAMIPRIL HEXAL may need to be withdrawn (see “CONTRA-INDICATIONS”).
- In acute myocardial infarction, patients may develop persistent hypotension and/or impaired renal function.
- Hypotension in acute myocardial infarction - Treatment with RAMIPRIL HEXAL 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 13,33 kPa or lower or cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 15,99 kPa or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2,5 mg if systolic blood pressure is 13,33 kPa or lower. If hypotension persists (systolic blood pressure less than 11,99 kPa for more than 1 hour) then RAMIPRIL HEXAL should be withdrawn.
- Bone marrow depression - Increased risk of agranulocytosis and neutropenia.
- Diabetes mellitus - Increased risk of hyperkalaemia, as well hypoglycaemia may occur.
- Hyperkalaemia - RAMIPRIL HEXAL may cause an increase in serum potassium levels.
- Renovascular disease – RAMIPRIL HEXAL 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 RAMIPRIL HEXAL should only be used under specialist supervision. The elderly, patients with peripheral vascular diseases or generalised atherosclerosis may have asymptomatic renovascular disease (see “DOSAGE AND DIRECTIONS FOR USE”).

- Renal artery stenosis, bilateral or in one kidney or renal transplant - Increased risk of renal function impairment which may lead to increase in 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 - Decreased elimination of RAMIPRIL HEXAL resulting in an increased risk of hyperkalaemia. These patients may require lower doses.
- Anaphylactoid reactions have occurred in patients using ACE inhibitors during desensitising protocols involving for example, hymenoptera venom.
- Anaphylactoid reactions have been reported in patients exposed to either high flux membrane dialysis or low-density lipoprotein apheresis with dextran sulfate absorption.
- Hypersensitivity/angioedema - If angioedema of the face, extremities, lips, tongue, glottis and/or larynx is observed in patients treated with RAMIPRIL HEXAL, RAMIPRIL HEXAL 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 involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate emergency therapy should be administered. This may include the administration of adrenaline 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. These patients should never receive any RAMIPRIL HEXAL again.
- RAMIPRIL HEXAL causes a higher rate of angioedema in black patients than in non-black patients.
- Safety and efficacy in children has not been established.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene and amiloride may lead to hyperkalaemia, which may be severe and lead to cardiac conduction abnormalities, dysarrythmias and cardiac arrest.
- Myocardial infarction and cerebrovascular accidents may be due to severe falls in blood pressure in high-risk patients e.g. those with ischaemic heart disease or cerebrovascular disease.
- In volume depleted patients or patients with ischaemic heart disease or cerebrovascular disease, therapy should be monitored especially when the dose of RAMIPRIL HEXAL or diuretic is adjusted.
- If hypotension occurs, the patient should be placed in the supine position and if necessary receive an intravenous infusion of 0,9 % saline.
- Increases in blood urea and serum creatinine have been seen in patients with no apparent pre-existing vascular disease, especially when RAMIPRIL HEXAL has been given concomitantly

with a diuretic. Dosage reduction or discontinuation of RAMIPRIL HEXAL or the diuretic may be required.

- Signs of facial or extremity swelling or difficulty in swallowing or breathing, required immediate medical attention, because of the risk of angioedema.
- Caution when driving or performing tasks requiring alertness because of possible dizziness.
- In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, RAMIPRIL HEXAL may block angiotension II formation secondary to complementary rennin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

**INTERACTIONS:**

**Concomitant use of RAMIPRIL HEXAL with** :

- Diuretics, alcohol and hypotension-producing medications – 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 “DOSAGE AND DIRECTIONS FOR USE”).
- Indomethacin and nonsteroidal anti-inflammatory medicines (NSAIDs) - Reduce the antihypertensive effects of RAMIPRIL HEXAL. Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with RAMIPRIL HEXAL.
- Potassium supplements or potassium sparing diuretics such as spironolactone, triamterene or amiloride - Concurrent administration may result in hyperkalaemia.
- Lithium - Increases in lithium concentrations have been reported. Frequent monitoring of serum lithium concentrations is recommended.

**PREGNANCY AND LACTATION:**

Use of RAMIPRIL HEXAL limited to the first trimester does not appear to present a significant risk to the foetus, but foetal exposure after this time has been associated with teratogenicity and severe toxicity in the foetus and newborn, including death. RAMIPRIL HEXAL crosses the placenta. Foetal exposure to ACE inhibitors during the second and third trimester can cause hypotension, renal failure, anuria, skull hypoplasia, hyperkalaemia and oliguria. Oligohydramnios may occur resulting in pulmonary hypoplasia, limb contractures and craniofacial deformation. Infants who have been exposed *in utero* to RAMIPRIL HEXAL should be closely monitored. Peritoneal dialysis may be of some benefit in the clearance of RAMIPRIL HEXAL from the neonatal circulation.
Safety in lactation has not been established.

**DOSAGE AND DIRECTIONS FOR USE:**

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

**Hypertension:**

***Adults****:*

Initial dose in patients not on diuretics is 2,5 mg RAMIPRIL HEXAL . The dose should be adjusted according to blood pressure response. The usual effective maintenance dose is 5 mg, given once a day with a maximum of 10 mg per day.

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.

**Post-myocardial infarction*:***

Initial dose is 2,5 mg RAMIPRIL HEXAL twice daily for 2 days, initiated in hospital three to ten days after acute myocardial infarction if the patient manifests with evidence of heart failure and is haemodynamically stable. If well tolerated, increase the dose to 5 mg RAMIPRIL HEXAL twice daily. If patients are unable to tolerate 2,5 mg initially, then 1,25 mg RAMIPRIL HEXAL twice daily may be given initially and later increased to 2,5 mg twice daily. Adjustments should be based on clinical response.

**Non-diabetic and diabetic nephropathy*:***

***Recommended initial dose***:

1,25 mg RAMIPRIL HEXAL once daily.

Depending on how the patient tolerates the medicine, the dose should be increased. It is recommended that the dose, if increased, be doubled at intervals of 2 to 3 weeks.

***Maximum permitted daily dose***:

10 mg RAMIPRIL HEXAL.

In patients pre-treated with a diuretic, consideration must be given to discontinuing the diuretic for at least 2 to 3 days or depending on the duration of action of the diuretic, longer, before starting treatment with RAMIPRIL HEXAL, or at least, to reducing the diuretic dose.

**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 RAMIPRIL HEXAL, diuretics should be discontinued 2 to 3 days before beginning therapy with RAMIPRIL HEXAL. In patients where diuretic therapy cannot be discontinued, treatment with RAMIPRIL HEXAL should be initiated with a reduction in diuretic dose. Subsequent dosage adjustments will depend on the therapeutic response. If required, diuretic therapy may be resumed.

***Renal impairment****:*
RAMIPRIL HEXAL is not recommended for use in dialysis patients.

***To reduce the risk of myocardial infarction, stroke or cardiovascular death****:*
The recommended initial dose is 2,5 mg RAMIPRIL HEXAL once daily. Depending on the tolerability, the dose is gradually increased. The increase should be implemented by doubling the dose after one week of treatment. Three weeks later, it should be doubled again to the usual maintenance dose of 10 mg RAMIPRIL HEXAL once daily.

RAMIPRIL HEXAL is not affected by the presence of food. RAMIPRIL HEXAL should be administered as a single daily dose at approximately the same time every day.

**SIDE EFFECTS:**

**Haematological*:***
***Less frequent****:* Decreases in white blood cell count, haemoglobin and haematocrit, bone marrow depression, anaemia, thrombocytopenia, agranulocytosis, haemolytic anaemia.

**Cardiovascular*:***
***Less frequent****:* Orthostatic effects (including hypotension), myocardial infarction, cerebrovascular accident, palpitations, tachycardia.

**Neurological*:***
***More frequent****:* Dizziness, headache, fatigue.
***Less frequent****:* Mood alterations, mental confusion, paraesthesia, vertigo, sleep disturbances.

**Endocrine/metabolic*:***
***Less frequent****:* Hyperkalaemia, hyponatraemia, increases in blood urea, increases in serum creatinine.

**Gastrointestinal*:***
***More frequent****:* Diarrhoea, nausea.

***Less frequent**:* Abdominal pain, indigestion, dry mouth, pancreatitis, vomiting, taste disturbances.

**Kidney/genitourinary*:***
***Less frequent**:* Uraemia, oligouria, anuria, renal dysfunction, acute renal failure, impotence.

**Liver/hepatic*:***
***Less frequent**:* Hepatitis (hepatocellular or cholestatic) jaundice, increases in liver enzymes, increases in serum bilirubin.

**Musculoskeletal*:***
***Less frequent**:* Asthenia.

**Respiratory*:***
***More frequent**:* Cough.
***Less frequent**:* Bronchospasm, rhinitis, sinusitis.

**Skin*:***
***Less frequent**:* Rash, urticaria, diaphoresis, alopecia, pruritus, psoriasis, severe skin disorders including pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme.

**Other*:***
***Less frequent***: Hypersensitivity/angioedema reactions: Angioedema of the face, which may be fatal, extremities, lips, tongue, glottis and/or larynx and intestinal angioedema. A symptom complex has been reported which may include fever, vasculitis, myalgia, arthritis/arthralgia, a positive antinuclear antibodies (ANA), elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

(See “SIDE EFFECTS" and "WARNINGS AND SPECIAL PRECAUTIONS”).

**Symptoms of overdose*:***
Severe hypotension, electrolyte disturbances and renal failure.

**Treatment overdose*:***

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. RAMIPRIL HEXAL is removable by haemodialysis.

**IDENTIFICATION:**

Ramipril Hexal 2,5: White, oblong, biplane with facet, both sides with breaking notch. Embossment one sided 'R 2.5'.
Ramipril Hexal 5 : White, oblong, biplane with facet, both sides with breaking notch. Embossment one sided 'R 5'.

**PRESENTATION:**

The tablets are packed into aluminium/aluminium blister strips containing 30 or 1000 tablets.
or
The tablets are packed in white HDPE containers containing 30 tablets.

**STORAGE INSTRUCTIONS:**

Store in a well-closed container at or below 25 °C. Protect from light.

The medicine must not be used after the expiry date printed on the pack.

**KEEP OUT OF THE REACH OF CHILDREN**.

**REGISTRATION NUMBERS:**

| | |
|---|---|
| Ramipril Hexal 2,5: | 37/7.1.3/0511 |
| Ramipril Hexal 5 : | 37/7.1.3/0512 |

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:**

Sandoz SA (Pty) Ltd[1]
72 Steel Road
Spartan
Kempton Park, 1619
South Africa

**DATE OF PUBLICATION OF THIS PACKAGE INSERT:**

08.04.2005

**Additional countries registration details:**

| *Country* | *Product name* | *Scheduling status (or Category of distribution)* | *Registration number* |
|---|---|---|---|
| **Botswana** | Ramipril-Hexal 2,5 | S2 | BOT1101799 |
| | Ramipril-Hexal 5 | S2 | BOT1101797 |
| **Namibia** | Ramipril-Hexal 2,5 | NS2 | 09/7.1.3/0071 |
| | Ramipril-Hexal 5 | NS2 | 09/7.1.3/0072 |

***ATC code:*** C09AA05 - Ace inhibitors, plain

**Name and address of manufacturer**

Salutas Pharma GmbH

Otto–von–Guericke allee 1, Barleben, Germany

or

LEK S.A,

16 Podlipie Str, 95-010 Strykow, Poland

[1]Company Reg. No.: 1990/001979/07