Professional Information for RENICARD 50

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

RENICARD 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each RENICARD 50 film-coated tablet contains 50 mg losartan potassium.

Excipient with known effect:

Contains sugar: 25,5 mg lactose monohydrate per tablet.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Light pink, biconvex, oblong, film-coated tablet with score mark on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RENICARD 50 is indicated for:

- The treatment of hypertension.
- Renal protection in type 2 diabetic patients with hypertension and proteinuria.

4.2 Posology and method of administration

Posology

Hypertension:

The usual starting and maintenance dose is 50 mg once daily for most patients. The maximum antihypertensive effect is achieved 3 – 6 weeks after initiation of therapy. The dose may be increased to 100 mg once daily.

For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see section 4.4).

No initial dosage adjustment is necessary for the elderly patients or for patients with renal impairment, including patients on dialysis. A lower dose should be considered for patients with a history of hepatic impairment (see section 4.4).

Renal protection in type 2 diabetic patients with hypertension and proteinuria:

The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response.

RENICARD 50 may be administered with other antihypertensive medicines (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting medicines) as well as with insulin and other commonly used hypoglycaemic medicines (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

Method of administration

RENICARD 50 may be administered with or without food.

4.3 Contraindications

- Hypersensitivity to losartan potassium or any of the ingredients of RENICARD 50 listed in section 6.1.
- A history of angioedema related to previous therapy with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), such as RENICARD 50: These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 mL/min) or for patients with hepatic impairment.
- Concomitant use of angiotensin receptor blockers with fluoroquinolones in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min) and in elderly patients.
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis, left ventricular outflow track obstruction.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.
- Thiazide diuretics in (fixed dose) combination with RENICARD 50 should not be given to patients with Addison’s disease. This therapy is also contraindicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines.
- Lithium therapy: Concomitant administration with RENICARD 50 may lead to toxic blood concentrations of lithium.
- Pregnancy and lactation (see section 4.6).
- The concomitant use of RENICARD 50 with aliskiren-containing products is contraindicated (see section 4.4).
- Safety and efficacy have not been established in children.

4.4 Special warnings and precautions for use

If a woman is contemplating pregnancy or should a woman become pregnant while receiving RENICARD 50, the treatment must be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):

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 RENICARD 50 and aliskiren is therefore contraindicated (see section 4.3). RENICARD 50 should not be used concomitantly with aliskiren (see section 4.3).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Concomitant use with fluoroquinolones:

Concomitant use of angiotensin receptor blockers and fluoroquinolones 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 and angiotensin receptor blockers whether used separately and/or concomitantly.

Hypotension and electrolyte/fluid imbalance:

Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of RENICARD 50, or a lower starting dose should be used (see section 4.2).

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalaemia was higher in the group treated with losartan as compared to the placebo group (see section 4.8). Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a creatinine clearance between 30 – 50 mL/min should be closely monitored.

The concomitant use of potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other medicines that may increase serum potassium (e.g. trimethoprim-containing products) with RENICARD 50 is not recommended (see sections 4.3 and 4.5).

Hepatic impairment:

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a dose of 25 mg should be considered for patients with a history of hepatic impairment (see section 4.2).

Renal impairment:

As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction). As with other medicines that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with

bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. RENICARD 50 is contraindicated in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney (see section 4.3).

Renal transplantation:

There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism:

Patients with primary aldosteronism generally will not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore, the use of RENICARD 50 is not recommended.

Coronary heart disease and cerebrovascular disease:

As with any antihypertensive medicine, excessive blood pressure decreases in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

Heart failure:

In patients with heart failure, with or without renal impairment, there is - as with other medicines acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life-threatening cardiac dysrhythmias. Therefore, RENICARD 50 should be used with caution in these patient groups. The combination of losartan

with a beta-blocker should be used with caution.

Other warnings and precautions:

As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take RENICARD 50.

4.5 Interaction with other medicines and other forms of interaction

Other antihypertensive medicines may increase the hypotensive action of RENICARD 50. Concomitant use with other medicines which may induce hypotension as an adverse reaction (like tricyclic antidepressants, antipsychotics, baclofen and amifostine) may increase the risk of hypotension.

Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the active carboxy-acid metabolite. In a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50 %. It was found that concomitant treatment of losartan with rifampicin (inducer of metabolism enzymes) gave a 40 % reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).

As with other medicines that block angiotensin II or its effects, concomitant use of other medicines which retain potassium (e.g. potassium-sparing diuretics: amiloride, triamterene, spironolactone) or may increase potassium levels (e.g. heparin, trimethoprim-containing products), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable. See sections 4.3 and 4.4.

When angiotensin II antagonists are administered simultaneously with nonsteroidal anti-inflammatory drugs (NSAIDs) (i.e. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of angiotensin II antagonists or diuretics and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated, and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Clinical trial data have 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 (including acute renal failure) compared to the use of a single RAAS-acting medicine (see sections 4.3, 4.4, and 5.1).

Concomitant use of angiotensin receptor blockers and fluoroquinolones 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).

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established (see section 4.3). When pregnancy is planned or confirmed RENICARD 50 should be discontinued.

Medicines affecting the renin-angiotensin system, such as RENICARD 50, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnancy women. Women of childbearing age should ensure effective contraception.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

4.8 Undesirable effects

Infections and infestations

Frequent: Upper respiratory infection.

Psychiatric disorders

Frequent: Insomnia.

Nervous system disorders

Frequent: Headache, dizziness, vertigo.

Less frequent: Somnolence, sleep disorders, paraesthesia.

Cardiac disorders

Frequent: Palpitations, tachycardia.

Less frequent: Angina pectoris, syncope, atrial fibrillation, cerebrovascular accident.

Vascular disorders

Less frequent: Orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders

Frequent: Cough, pharyngitis, nasal congestion, sinus disorder.

Less frequent: Dyspnoea.

Gastrointestinal disorders

Frequent: Diarrhoea, nausea, abdominal pain, dyspepsia.

Less frequent: Obstipation.

Skin and subcutaneous tissue disorders

Less frequent: Rash.

Musculoskeletal and connective tissue disorders

Frequent: Back pain, muscle cramps.

Renal and urinary disorders

Frequent: Renal impairment, renal failure.

General disorders and administration site conditions

Frequent: Asthenia/fatigue, oedema/swelling, chest pain.

Investigations

Frequent: Hyperkalaemia, elevations of ALT, increase in blood urea, serum creatinine and serum potassium, hypoglycaemia.

The following adverse reactions have been reported in post-marketing experience. They are derived from spontaneous reports for which precise incidences cannot be determined, therefore the frequency is unknown:

Blood and lymphatic system disorders

Anaemia, thrombocytopenia.

Immune system disorders

Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue has been reported in patients treated with losartan; some of these patients previously experienced angioedema with ACE inhibitors and angiotensin receptor blockers.

Psychiatric disorders

Depression.

Nervous system disorders

Migraine, dysgeusia.

Ear and labyrinth disorders

Tinnitus.

Vascular disorders

Vasculitis, including Henoch-Schönlein purpura.

Gastrointestinal disorders

Vomiting.

Hepatobiliary disorders

Hepatitis, pancreatitis.

Skin and subcutaneous tissue disorders

Urticaria, pruritus, erythroderma, photosensitivity.

Musculoskeletal and connective tissue disorders

Myalgia, arthralgia, rhabdomyolysis.

Reproductive system and breast disorders

Erectile dysfunction, impotence.

General disorder and administration site conditions

Malaise.

Investigations

Liver function abnormalities, hyponatraemia.

Description of selected adverse reactions

Renal and urinary disorders:

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in patients at risk. These changes in renal function may be reversible upon discontinuation of therapy (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of RENICARD 50 is important. It allows continued monitoring of the benefit/risk balance of RENICARD 50. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

The symptoms of an overdosage of RENICARD 50 would be hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Neither RENICARD 50 nor the active metabolite can be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1.3 Other hypotensives.

Pharmacotherapeutic group: Angiotensin II antagonists, plain.

ATC code: C09CA01.

Losartan is a nonpeptide angiotensin II receptor antagonist with high affinity and selectivity for the AT_1 receptor, without binding to or blocking other hormone receptors or ion channels important in cardiovascular regulation. Angiotensin II is a potent vasoconstrictor, a primary active hormone of the renin-angiotensin system, and a major determinant of the pathophysiology of hypertension. Losartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by inhibiting the binding of angiotensin II to the AT_1 receptor.

Losartan is a specific antagonist of the angiotensin II receptor type AT_1. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity during losartan administration. A 2 – 3-fold increase in angiotensin II in plasma comes as a result of increases in plasma renin activity. However, antihypertensive activity and suppression of plasma aldosterone concentration are apparent, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, plasma renin activity and angiotensin levels declined.

5.2 Pharmacokinetic properties

Following oral administration, bioavailability is approximately 33 %. It undergoes first-pass metabolism to form an active carboxylic acid metabolite, (which has greater pharmacological activity than losartan) and some inactive metabolites. About 14 % of an intravenously or orally administered dose is converted to its active metabolite. The mean peak concentrations of losartan and its active metabolite are reached in 1 hour and 3 – 4 hours, respectively. Both losartan and the carboxylic acid metabolite are greater than, or equal to 99 % bound to plasma proteins. The distribution volume of losartan is 34 litres. The terminal half-life of losartan is 2 hours and of its active metabolite is 6 – 9 hours.

Losartan is excreted in the urine, and in the faeces, as unchanged drug and metabolites. Following oral dosing, about 35 % of the dose is excreted in the urine and about 60 % in the faeces. Neither losartan nor the active metabolite can be removed by haemodialysis.

Plasma concentrations of losartan are not altered in patients with impaired renal function and a creatinine clearance above 10 mL/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in patients on haemodialysis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460)

Lactose monohydrate

Pregelatinised starch

Purified talc (E553)

Magnesium stearate (E572)

Opadry Pink (consisting of hypromellose [E464], titanium dioxide [E171], macrogol [E1521], talc [E553], iron oxide red [E172]).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C in a dry place.

Protect from light.

Keep the blister strips in outer carton until required for use.

6.5 Nature and contents of container

Aluminium/PVC blister strips of 10 tablets. Three strips will be packed in an outer carton.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unichem SA (Pty) Ltd

San Domenico

Ground Floor, Unit G4

10 Church Street

Durbanville

7551 Cape Town

Tel: +27 21 531 0436

8. REGISTRATION NUMBER

A39/7.1.3/0580

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