SCHEDULING STATUS:

S3

PROPRIETARY NAME (and dosage form):

RAMIWIN 1,25 mg (capsules)

RAMIWIN 2,5 mg (capsules)

RAMIWIN 5 mg (capsules)

COMPOSITION:

Per capsule: 1,25 mg, 2,5 mg and 5 mg ramipril as active substance.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Hypotensives

PHARMACOLOGICAL ACTION:

Ramipril is a long acting inhibitor of the angiotensin converting enzyme (ACE).

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.

Ramipril increases plasma renin activity and decreases plasma concentrations of angiotensin II and aldosterone.

The beneficial haemodynamic effects are caused by ACE inhibition and the consequent reduction in angiotensin II results in dilation of peripheral vessels and reduction in vascular resistance.

Ramipril binds to ACE at both plasma and tissue levels.

Angiotensin converting enzyme is identical to 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 these mechanisms contribute to the hypotensive activity of ramipril too, and may be at least co-responsible for certain adverse reactions, e.g. dry cough.

Following oral administration, ramipril is rapidly absorbed from the gastrointestinal tract, and peak

plasma concentrations of ramipril are reached within one hour. Ramipril is a prodrug, which is converted in the liver to its diacid metabolite, ramiprilat, by cleavage of an ester group. Peak plasma concentrations of ramiprilat are reached two to four hours after drug intake. Based on the urinary recovery of ramipril and its metabolites the extent of absorption is estimated to be 30 per cent to 60 per cent.

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

Plasma concentrations of ramiprilat decline in a polyphasic manner. The effective half-life of ramiprilat after multiple once daily administration of ramipril is 13 to 17 hours for 5 to 10 mg ramipril and several times longer for lower doses such as 1,25 to 2,5 mg ramipril.

The prolonged half-life at low dosages is due to a high fraction of the metabolite being bound to the angiotensin converting enzyme at low plasma concentrations and thus a slow dissociation of this enzyme inhibitor complex. However, with high dosages a shorter half-life due to a higher free fraction leading to easier dissociation is observed.

Steady-state plasma concentrations of ramiprilat after once daily dosing of the usual doses of ramipril are reached at about treatment day four.

Ramipril is almost completely metabolised and the metabolites are excreted mainly via the kidneys. Besides the bioactive metabolite ramiprilat, further inactive metabolites have been identified, i.e. diketopiperazine ester, diketopiperazine acid, and conjugates.

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

The protein binding of ramipril is about 73 per cent and of ramiprilat about 56 per cent.

“Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure.” (Lancet 1993; 342: 821-828, October 1993) AIRE (Acute Infarction Ramipril Efficacy) study: An international multicentre study including 2006 patients, 1004 randomised to ramipril and 982 to placebo.

All patients aged at least 18 years admitted to coronary care, intensive care, all general medical units with a definite acute myocardial infarction (AMI) and clinical evidence of heart failure at any time after the index AMI, were eligible.

Patients with severe heart failure (usually NYHA grade IV), heart failure of primary valvular or congenital aetiology, unstable angina, or any of the recognised contra-indications to ACE-inhibitor treatment, were excluded from the study. When ramipril was administered to patients with clinical evidence of heart failure on the third to ninth day after a myocardial infarction for an average of fifteen months, a reduction in all-cause mortality was demonstrated. The final analysis shows a total mortality of 11 per cent in the ramipril group and 14 per cent in placebo. This is calculated as an overall reduction in the risk of death of 27 per cent which was statistically significant. However, the cause of death was not supplied in the study. Most patients (88 per cent) were not on digoxin, and only 58 per cent received a diuretic at the start of the study. Also, there was no separate analysis of patients who only had transient congestive cardiac failure.

In patients with non-diabetic or diabetic overt nephropathy, the mode of action (pharmacodynamics) is that ramipril decreases the rate of progression of renal insufficiency and of the development of end-stage renal failure and therewith the need for dialysis or renal transplantation. In patients with diabetic nephropathy and hypertension, ramipril reduces albumin excretion and the decline in glomerular filtration rate.

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.

CONTRA-INDICATIONS:

Hypersensitivity to ramipril and starch. History of angioneurotic oedema.

Ramipril is not recommended for use in children.

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.
Concomitant use of ACE inhibitors with fluoroquinolones is contraindicated in patients with moderate to severe renal impairment.

WARNINGS:

Should a woman become pregnant while receiving an ACE-inhibitor, the treatment should be stopped promptly and switched to a different medicine. Should a woman contemplate pregnancy, the doctor should consider alternative medication.

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

Treatment with RAMIWIN may impair the ability to drive or operate machinery, particularly at the start of treatment, when changing over from other preparations and during concomitant use of alcohol.

In patients with impaired liver function, the metabolism of the parent compound ramipril 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 ramipril in patients with impaired liver function is not recommended.

Concomitant use of fluoroquinolones and ACE inhibitors may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see CONTRA-INDICATIONS). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors whether used separately

and/or concomitantly.

DOSAGE AND DIRECTIONS FOR USE:

RAMIWIN should be taken with half a glass of liquid during or after meals.

Hypertension:

Administration of RAMIWIN to hypertensive patients results in a reduction of both supine and erect blood pressure. The antihypertensive effect is evident within one to two hours after intake of the medicine, peak effect occurs three to six hours after intake, and has been shown to be maintained for at least 24 hours at recommended doses. The dose range is 2,5 mg to 10 mg RAMIWIN in a single daily dose.

The recommended initial dosage in patients not on diuretics is 2,5 mg RAMIWIN once a day. Dosage should be increased to 5 mg RAMIWIN and up to a maximum of 10 mg RAMIWIN once a day at intervals of one to two weeks based on patient response.

A maximum dose of 10 mg should not be exceeded.

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of RAMIWIN. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with RAMIWIN to reduce the likelihood of hypotension. In case the diuretic therapy cannot be discontinued, the initial dose of RAMIWIN should be 1,25 mg.

Post-myocardial infarction:

The treatment with RAMIWIN should be initiated in hospital 3 to 10 days after an acute myocardial infarction if the patient manifests with evidence of heart failure and is haemodynamically stable. The recommended dosage is 2,5 mg RAMIWIN twice daily for two days. If well tolerated, increase the dose to 5 mg RAMIWIN twice daily.

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

Non-diabetic and diabetic nephropathy:

Recommended initial dose: 1,25 mg RAMIWIN 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 RAMIWIN.

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 RAMIWIN, or at least, to reducing the diuretic dose.

Dosage adjustment in renal impairment:

Ramipril is not recommended for use in dialysis patients.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

The most frequently reported side-effects are nausea, dizziness and headache. A dry cough has been reported.

Cardiovascular system:

Hypotension may occur after the initial dose of RAMIWIN, as well as after increasing the dose of RAMIWIN.

Symptomatic hypotension (i.e. headache, tiredness, palpitations, tinnitus) accompanied by dizziness, nausea and a feeling of weakness can be observed in salt/volume depleted patients such as those treated with diuretics or patients on dialysis, as well as in patients with severe congestive heart failure. Syncope has been observed.

In patients with concomitant congestive heart failure with or without renal insufficiency, excessive hypotension has been observed and may be associated with oliguria or azotemia. In these patients therapy should be started under close medical supervision, and at a reduced starting dose.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of physiological saline.

Renal function:

Treatment with RAMIWIN may impair renal function.

Patients with renal insufficiency may require reduced initial doses of RAMIWIN and their renal function should be closely monitored. There is a risk of impairment of renal function particularly in patients with congestive heart failure or renovascular disease (bilateral renal artery stenosis or unilateral renal artery stenosis in the single kidney), in patients with pre-existing impairment of renal function, as well as in kidney transplant patients.

Some patients with no apparent pre-existing renal disease may develop increases in blood urea, proteinuria and serum creatinine when RAMIWIN is given.

In patients with renal insufficiency there is a risk of hyperkalaemia. Decrease in serum sodium can also occur.

Liver function:

As RAMIWIN is a prodrug metabolised in the liver to its active moiety, particular caution and close monitoring should be applied in patients with liver impairment. The metabolism of the parent compound and therefore the formation of the bioactive metabolite ramiprilat may be decelerated, resulting in markedly elevated plasma levels of the parent-compound due to the diminished activity of esterases in the liver.

Surgery/Anaesthesia:

In patients undergoing surgery or during anaesthesia with agents producing hypotension, RAMIWIN 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 and proteinuria:

Regular monitoring of white blood cell counts and protein levels in urine should be performed in patients with collagen vascular disease, such as lupus erythematosus and systemic sclerosis, in particular where associated with impaired renal function and concomitant therapy with drugs like corticosteroids and antimetabolites.

Hyperkalaemia:

Elevated serum potassium may occur in hypertensive patients.

Risk factors for the development of hyperkalaemia include renal insufficiency and the concomitant use of agents to treat hypokalaemia as well as potassium sparing diuretics.

Gastrointestinal tract:

Gastrointestinal disorders, e.g. nausea, diarrhoea or gastric pain may occur but these reactions are often transient.

Taste disturbances may occur.

Angioneurotic oedema:

Angioneurotic oedema may occur during therapy with ACE-inhibitors including RAMIWIN.

If laryngeal stridor or angio-oedema of the face, tongue or glottis occurs, treatment with RAMIWIN must be discontinued and appropriate therapy instituted immediately.

Allergic reactions:

Hypersensitivity reactions accompanied by pruritus, rash and sometimes fever may occur, but may resolve spontaneously after withdrawal of RAMIWIN.

Laboratory values:

Increases in blood urea and serum creatinine may occur, particularly in patients with renal insufficiency or in patients pre-treated with a diuretic. Elevation of serum potassium may occur, since RAMIWIN decreases aldosterone secretion.

Potassium sparing diuretics such as spironolactone, amiloride, triamterene or potassium

supplements should therefore be avoided.

Increases in liver enzymes and/or bilirubin.

Changes in blood picture: decrease in haemoglobin; leukopenia and thrombocytopenia.

Interactions:

Concomitant use of ACE inhibitors 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 CONTRA-INDICATIONS).

Combination with diuretics or other antihypertensives may potentiate the antihypertensive response to RAMIWIN. Potassium sparing diuretics such as spironolactone, amiloride, triamterene or potassium supplements increase the risk of hyperkalaemia. RAMIWIN may attenuate potassium loss caused by thiazide-type diuretics. Therefore, if concomitant use of these agents is indicated they should be given with caution and with frequent monitoring of serum potassium.

Concomitant therapy with lithium may increase the serum lithium concentration.

Interaction between ACE-inhibitors and non-steroidal anti-inflammatory agents have been reported. The antihypertensive effects of the ACE-inhibitors may be decreased.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In case of overdosage, excessive hypotension is to be expected. Treatment should include volume expanders.

IDENTIFICATION:

1,25 mg: yellow and white capsules.

2,5 mg: medium orange and white capsules.

5 mg: scarlet and white capsules.

PRESENTATION:

Cartons containing one or more blister packs with 10 capsules each.

STORAGE INSTRUCTIONS:

Store below 25 °C.

The medicine must not be used after the expiry date printed on the pack. Keep out of reach of children.

REGISTRATION NUMBERS:

RAMIWIN 1,25 mg: W/7.1.3/232

RAMIWIN 2,5 mg: W/7.1.3/233

RAMIWIN 5 mg: W/7.1.3/234

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