Core Safety Profile

Active substance: Ramipril + Furosemide
Pharmaceutical form(s)/strength: Capsules, 5mg/20mg
Capsules, 5mg/40mg
P-RMS: AT/H/PSUR/0008/002
Date of FAR: 14.11.2011
4.3 Contraindications

- Hypersensitivity to the active substances, sulfonamides, other ACE inhibitors (ACE = angiotensin converting enzyme) or one of the other ingredients
- Hypersensitivity to the active substance, to any of the excipients or any other ACE (Angiotensin Converting Enzyme) inhibitors (see section 6.1)
- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or AIIRAs)
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5)
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney
- Ramipril must not be used in patients with hypotensive or haemodynamically unstable states.
- clinically relevant electrolyte disorders (e.g. hypokalaemia, hyponatraemia)
- 2nd and 3rd trimester of pregnancy (see sections 4.4 and 4.6)
- lactation period (see section 4.6)
- hypovolaemia or dehydration
- kidney failure with anuria, if the patients do not respond to therapy with furosemide
- precomatose and comatose stage in connection with hepatic encephalopathy

4.4 Special Warnings and Precautions for Use

General warnings when starting treatment with /.../: Before starting treatment with /.../, any dehydration, hypovolaemia or salt deficiency must first be controlled (in patients with heart failure these measures must be weighed carefully against the risk of volume overload, however).

Regular monitoring of the serum electrolytes (esp. potassium, sodium, calcium, bicarbonate, creatinine, urea and uric acid as well as the blood sugar level is indicated throughout the entire duration of treatment.

Urinary flow must be ensured at all times during the treatment, otherwise the increase in urinary output can cause symptoms.

Ramipril:

Special patient groups

Pregnancy: Therapy with ACE inhibitors such as ramipril or angiotensin-II receptor antagonists (AIIRAs) should not be started during pregnancy. If continued treatment with an ACE inhibitor/AIIRA is considered unavoidable, the patient should be switched to an alternative antihypertensive therapy with an established safety profile for use during pregnancy before a planned pregnancy. As soon as pregnancy has been diagnosed, treatment with an ACE inhibitor/AIIRA should be discontinued immediately and an alternative antihypertensive treatment initiated if necessary (see sections 4.3 and 4.6).

- patients with risk of hypotension
- patients with increased activity of the renin-angiotensin-aldosterone system

In patients with an increased activity of the renin-angiotensin-aldosterone system there is a risk of sudden marked drop in blood pressure and deterioration of the kidney function occurring due to ACE inhibition. This applies in particular if an ACE inhibitor is administered for the first time or concurrently with a diuretic for the first time, or when the dosage is increased.
A significant activation of the renin-angiotensin-aldosterone system that requires medical supervision with monitoring of the blood pressure must be expected e.g. in the following patients:

- patients with severe hypertension,
- patients with decompensated heart failure,
- patients with haemodynamically relevant left-ventricular in- or outflow obstruction (e.g. aortic or mitral valve stenosis),
- patients with unilateral renal artery stenosis and a second functional kidney,
- patients with manifest or latent fluid or salt deficiency (including patients on diuretics),
- patients with liver cirrhosis and/or ascites,
- patients undergoing major surgery or during anaesthesia with drugs that can cause hypotension.

- patients with transient or persistent heart failure after myocardial infarction
- patients with a risk of myocardial or cerebral ischemia during acute hypotension

In the initial phase of treatment, the patient must be kept under close medical supervision.

Elderly patients
See Section 4.2.

**Surgery**
Treatment with /…/ should be discontinued one day before surgery, if possible.

**Monitoring of kidney function**
Kidney function should be monitored before and during treatment, and the dose should be adjusted accordingly, especially in the first weeks of treatment. Patients with impaired kidney function (see section 4.2) require particularly close monitoring. In patients with decompensated heart failure or after kidney transplantation, in particular, there is a risk of impaired kidney function.

**Angioneurotic oedemas**
The occurrence of angioneurotic oedemas has been reported in patients on ACE inhibitors, especially ramipril (see section 4.8).

Treatment must be discontinued if an angioneurotic oedema occurs. Emergency treatment must be initiated immediately. The patient must be observed for at least 12 to 24 hours and must not be discharged until the symptoms have disappeared completely.

Intestinal angioneurotic oedemas have been reported in patients on ACE inhibitors (see section 4.8). These patients suffered from abdominal pain (with or without nausea or vomiting).

**Anaphylactic reactions during hyposensitisation**
During ACE inhibition, the probability and severity of anaphylactic and anaphylactoid reactions to insect toxins and other allergens is increased. During hyposensitisation, temporary discontinuation of /…/ should be considered.

**Hyperkalaemia**
The occurrence of hyperkalaemia has been observed in some patients on ACE inhibitors. Patients with a risk of hyperkalaemia include patients with kidney failure, elderly patients (> 70 years), untreated or inadequately treated diabetics or patients using potassium salts, potassium-sparing diuretics and other substances that elevate the serum potassium level, or patients with dehydration, acute cardiac decompensation or metabolic acidosis. If concurrent use of the above substances is indicated, regular monitoring of the serum potassium level is required (see section 4.5).
Neutropenia/agranulocytosis
Neutropenia/agranulocytosis as well as thrombocytopenia and anaemia have been observed in rare cases, and bone marrow depression has also been reported. Monitoring of the leukocyte counts is recommended to detect a possible leukopenia. More frequent monitoring is advised in the early phase of treatment and in patients with impaired kidney function, in patients with concurrent collagenosis (e.g. lupus erythematoses or scleroderma), and in all patients concurrently on treatment with other drugs that can change the blood count (see section 4.5 and 4.8).

Ethnic differences
ACE inhibitors cause angioneurotic oedemas more commonly in patients with black skin colour than in patients of other skin colour.
As with other ACE inhibitors, it is possible that ramipril will be less effective in lowering the blood pressure in black patients than in other patients, possibly due to the higher prevalence of hypertension with low renin level in hypertensive patients with black skin.

Cough
Coughing has been reported during therapy with ACE inhibitors. Typically, the cough is non-productive, persistent, and disappears after withdrawal of the therapy. Coughing induced by an ACE inhibitor should be taken into consideration in the differential diagnosis of the cough.

Furosemide:
Particularly close supervision and medical monitoring is required in cases of:

- hypotension
- manifest or latent diabetes mellitus
- gout
- hepatorenal syndrome
- urinary flow obstruction (e.g. in the case of hypertrophy of the prostate, hydronephrosis, urethral stenosis)
- hypoproteinaemia
- patients at particular risk in the case of an unintentionally strong drop in blood pressure, e.g. patients with cerebrovascular circulation disorders or coronary heart disease
- nephritic syndrome: Due to the risk of increased side effects, the medication must be dosed cautiously

Due to strong effectiveness (dehydration with dizziness and light-headedness), furosemide preparations must only be used for the treatment of hypertension in patients with healthy kidneys after a caution risk-benefit assessment.
The weight loss caused by increased urinary excretion should not exceed 1 kg/day, regardless of the extent of urinary excretion.
In patients who develop hypovolaemia during furosemide therapy or in the case of dehydration, concurrent administration of non-steroid anti-inflammatory drugs can trigger acute kidney failure.
Since the use of furosemide can cause hypokalaemias, a high-potassium diet (lean meat, potatoes, bananas, tomatoes, cauliflower, spinach, dried fruits, etc.) is always expedient. Thiamine should be substituted during longer use of furosemide. A commonly observed deficiency due to the increased furosemide-related renal elimination causes deterioration of heart function.

Combined use with risperidone:
In placebo-controlled studies with risperidone in elderly patients with dementia, an increased mortality rate was observed in patients treated with furosemide and risperidone (7.3%: mean age 89 years; range 75-97 years) versus patients treated only with risperidone (3.1%: mean age 84 years; range: 70-96 years) or furosemide (4.1%: mean age 80 years; range: 67-90 years). The use of risperidone together with other diuretics (esp. thiacide diuretics at low
dosages) was not associated with comparable results. A pathophysiological mechanism to explain these findings was not identified. Before use, a risk-benefit assessment for this combination or combined treatment with other highly effective diuretics should be carried out. An increased mortality rate was not observed in patients using other diuretics in combination with risperidone. Irrespective of the treatment, dehydration was a general risk factor for mortality and must therefore be avoided in elderly patients with dementia (see section 4.3).

4.5 Interactions with other Medicinal Products and other Forms of Interaction

Contraindicated combinations

Extracorporeal treatments involving contact between blood and negatively charged surfaces, such as haemodialysis or haemofiltration with certain high-flux membranes (e.g. polycrystal nitrile membranes) and LDL apheresis with dextrane sulphate, are contraindicated due to the increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is necessary, use of a different dialysis membrane or another class of antihypertensive drug should be considered.

Furosemide can potentiate the ototoxicity of aminoglycosides and other ototoxic drugs. Since this can cause irreversible hearing damage, these drugs must not be used in combination with furosemide unless medically absolutely indicated.

Combinations requiring particular caution

*Potassium salts, heparin, potassium-sparing diuretics and other substances that elevate the serum potassium level (such as angiotensin-II antagonists, trimethoprim, tacrolimus, cyclosporine):* Hyperkalaemia may occur. Therefore the serum potassium level must be monitored closely.

*Antihypertensive drugs (e.g. diuretics) and other blood pressure-lowering substances (e.g. nitrates, tricyclical antidepressants, anaesthetics, acute alcohol intake, baclofene, alfuzosine, doxazosine, prazosine, tamsulosine, terazosine):* risk of drop in blood pressure may be increased.

*Vasopressory sympathomimetics and other substances (e.g. isoproterenol, dobutamine, dopamine, epinephrine) that can weaken the antihypertensive effect of ramipril:* Regular monitoring of the blood pressure is recommended.

*Allopurinol, immunosuppressive drugs, corticosteroids, procainamide, cytostatics and other drugs that may change the blood count:* increased probability of haematological reactions (see section 4.4).

*Lithium salts:* ACE inhibitors and furosemide can lower the lithium elimination rate, so that the toxic effect (risk of cardiotoxic and neurotoxic effects) of lithium may increase. Regular monitoring of the serum lithium level is required.

*Antihypertensives, diuretics or drugs with a blood pressure-lowering potential:* Combined with furosemide, a strong drop in blood pressure must be expected with these drugs. Massive drops in blood pressure and even shock as well as deterioration of the kidney functions (acute kidney failure in isolated cases) have been observed especially when an ACE inhibitor or angiotensin-II receptor antagonist was given for the first time or at a high dosage for the first time. If possible, the furosemide therapy should therefore be discontinued temporarily, or at least the dose should be reduced for three days, before the therapy with an ACE inhibitor or angiotensin-II receptor antagonist is started or the dosage is increased.
Antidiabetics, including insulin: Hypoglycaemia may occur. Regular monitoring of the blood sugar level is recommended.

Non-steroidal anti-inflammatory drugs and acetylsalicylic acid: A decrease in the antihypertensive effect of ramipril and furosemide must be expected. The toxic effect of salicylates may be enhanced by the furosemide component. Moreover, concurrent treatment with ACE inhibitors and NSAIDS can increase the risk of a kidney function disorder or acute kidney failure (especially if there is a risk of hypovolaemia or dehydration) and of an increase in serum potassium level.

Nephrotoxic or ototoxic antibiotics, cisplatin: During concurrent use with furosemide, the possibility of hearing damage must be expected. If forced diuresis with furosemide is intended during cisplatin treatment, furosemide must be given only at a low dose (e.g. 40 mg in patients with normal kidney function) and if the fluid balance is positive. Otherwise the nephrotoxicity of cisplatin may be enhanced.

Sucralfate: Oral sucralfates and furosemide should only be taken at intervals of 2 hours, as sucralfate inhibits furosemide absorption from the intestine and thus weakens its effect.

Phenytoin: Weakening of the effect of furosemide.

Glucocorticoids, carbenoxolone, liquorice in large quantities, laxative abuse, ACTH, salicylates, amphotericin B, penicillin G: Increased potassium losses due to the furosemide component.

Probenecide, methotrexate and other drugs that, like furosemide, are secreted mainly tubularly in the kidney: can weaken the effect of furosemide. Furosemide can reduce the renal elimination of these drugs. During high-dose treatment (especially with both furosemide and the other drug), this can cause elevated serum levels and a major risk of side effects from furosemide or the concomitant medication.

Cardiac glycosides, preparations that prolong the QT segment (e.g. certain anti-arrhythmic drugs): Certain electrolyte disorders (e.g. hypoglycaemia, hypomagnesaemia) can increase the toxicity of other substances (e.g. drugs that can trigger a prolongation of the QT interval).

Theophylline, curare-like muscle relaxants: Enhancement/prolongation of effect by furosemide.

Oral anticoagulants: an adjustment of the anticoagulant does may be necessary.

Antidiabetics, pressory amines (e.g. epinephrine, norepinephrine): Weakening of the effect of furosemide.

Nephrotoxic drugs: Furosemide can increase the nephrotoxic effects of these drugs (e.g. antibiotics such as aminoglycosides, cephalosporines, polymyxins). In patients treated concurrently with furosemide and high doses of certain cephalosporines, a deterioration of kidney function may occur.

Cyclosporine A: The concurrent use of furosemide and cyclosporine A is associated with an increased risk of arthritis urica, a form of hyperuricaemia caused by furosemide and an impairment of renal uric acid elimination due to cyclosporine.

Risperidone: Caution is required; a risk-benefit assessment should be carried out for the combination with furosemide or concomitant treatment with other highly effective diuretics prior to the treatment (see section 4.4).
Patients with a high risk of kidney damage due to x-ray contrast dye: During treatment of these patients with furosemide, a deterioration of kidney function after an examination with x-ray contrast dye occurred more commonly than in patients who only received intravenous fluids (hydration) before the examination with contrast.

Alcohol: The effect of alcohol is enhanced during treatment with /.../. Therefore the consumption of alcohol should be avoided during the treatment.

Table salt: A high supply of table salt may reduce the antihypertensive effect of /.../.

4.6 Fertility, pregnancy and lactation

Pregnancy

/.../ is not recommended during the first trimester of pregnancy (see section 4.4) and is contraindicated during the second and third trimester of pregnancy (see section 4.3).

Ramipril

As soon as pregnancy has been diagnosed, treatment with the ACE inhibitor should be discontinued immediately and alternative therapy initiated if necessary. The epidemiological evidence with regard to teratogenicity risk after exposure to an ACE inhibitor in the first trimester of pregnancy is not conclusive, but a slightly increased risk cannot be excluded. Unless continued treatment with an ACE inhibitor is considered unavoidable, the patient should be switched to an alternative antihypertensive therapy with an established safety profile for use during pregnancy before a planned pregnancy.

It is known that therapy with an ACE inhibitor/angiotensin-II receptor antagonist (AIIRA) during the second and third trimester of pregnancy has foetotoxic effects in humans (kidney function disorder, oligohydramnion, retardation of skull ossification) and can trigger toxic effects in the neonate (kidney failure, hypotension, hyperkalaemia). In the event of exposure to an ACE inhibitor as of the second trimester of pregnancy, ultrasound scans of the kidney function and skull are recommended. Neonates whose mothers took ACE inhibitors must be monitored closely with regard to hypotension, oliguria and hyperkalaemia (see also sections 4.3 and 4.4).

Furosemide

During pregnancy furosemide must only be used if absolutely indicated and only for a short time if medically absolutely necessary. Treatment during pregnancy requires monitoring of the foetal development.

Furosemide reaches 100% of the maternal serum concentration in the umbilical cord blood. So far no malformations in humans that might be associated with furosemide exposure have been reported. However, sufficient experience for a final assessment of a potential harmful effect on the embryo/foetus is not available. (see section 5.3) In the foetus, urine production in utero can be stimulated. Moreover, ototoxic effects and hypokalaemic alkalosis of the foetus are possible during use in late pregnancy.

Diuretics are not suitable for routine treatment of hypertension and oedema in pregnancy, as the impair perfusion of the placenta and thus intra-uterine growth.

If furosemide has to be used in the case of heart or kidney failure during pregnancy, electrolytes and haematocrit as well as development of the foetus must be monitored closely. There is also discussion of a displacement of bilirubin from its albumin binding and thus an increased risk of kernicterus with hyperbilirubinaemia due to furosemide.
Breastfeeding
Use of /.../ is contraindicated during the lactation period.

4.7 Effects on the Ability to Drive and Use Machines

Some side effects (e.g. symptoms of low blood pressure, such as dizziness) can impair the patient’s ability to concentrate and react and thus pose a risk in situations in which these abilities are particularly important (e.g. when driving a vehicle or operating machinery). This applies particularly at the beginning of treatment or when switching preparation.

4.8 Undesirable Effects

The incidence rates of side effects are based on the following categories:

Very common (≥ 1/10), common (≥ 1/100 to < 1/10), occasional (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), unknown (incidence not assessable on the basis of the available data).

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Unknown</th>
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</thead>
<tbody>
<tr>
<td><strong>Cardiac disorders</strong></td>
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<tr>
<td></td>
<td>Myocardial ischaemia including angina pectoris or tachycardia, arrhythmia, palpitations, peripheral oedemas</td>
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<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
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<td></td>
<td>Eosinophilia, thrombocytopenia</td>
<td>Decrease in leukocyte count (including neutropenia or agranulocytosis) or erythrocyte count, decreased haemoglobin level</td>
<td>Aplastic anaemia, haemolytic anaemia</td>
<td>Bone marrow depression, pancytopenia, haemoconcentration</td>
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<tr>
<td><strong>Nervous system disorders:</strong></td>
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<tr>
<td>Headache, dizziness</td>
<td>Vertigo, paraesthesias, loss of the sense of taste, taste disorders</td>
<td>Tremor, balance disorders</td>
<td>Confusion, lethargy</td>
<td>Cerebral ischaemia including ischaemic stroke and transitory ischaemic attacks, impairment of psychomotor skills, sensation of burning on the skin, disturbed sense of smell; in patients with liver failure,</td>
</tr>
</tbody>
</table>
### Eye disorders
- Disturbed vision, enhancement of an existing myopia including blurred vision
- Conjunctivitis

### Ear and the labyrinth disorders
- Disturbed hearing, tinnitus

### Respiratory, thoracic and mediastinal disorders:
- Dry irritable cough, bronchitis, sinusitis, dyspnoea
- Bronchospasm including exacerbation of bronchial asthma, swelling of the nasal mucosa

### Vascular disorders
- Hypotension, orthostatic drop in blood pressure, syncope
- Vascular stenosis, hypoperfusion, vasculitis
- Raynaud syndrome, increased disposition for thrombosis

### Gastro-intestinal disorders
- Inflammation of the gastrointestinal tract, digestive disorders, abdominal pain, dyspepsia, diarrhoea, nausea, vomiting
- Pancreatitis (in exceptional cases even fatal), elevation of pancreas enzymes, angio-neurotic oedema in the small intestine, epigastric pain including gastritis, obstruction, dry mouth
- Glossitis
- Stomatitis aphthosa

### Renal and urinary disorders:
- Kidney function disorders, including acute kidney failure, increased diuresis, exacerbation of an existing proteinuria, elevation of serum urea, elevation of serum creatinine
- Interstitial nephritis
- Acute urinary flow disorders in patients with partial urinary flow obstruction

### Skin and subcutaneous tissue
- Exanthema, especially maculo-
- Angio-neurotic oedema, in exceptional
- Onycholysis
- Toxic epidermal necrolysis, Stevens-
disorders: papulous cases
obstruction of the respiratory tract due to the angioneurotic oedema can be fatal; pruritus; hyperhidrosis, itchiness, urticaria, other rashes or bullous lesions, erythema multiforme, dermatitis exfoliativa, bullous pemphigoid, purpura, photosensitivity

Musculoskeletal disorders:
Muscle cramps, myalgia

Metabolism and nutrition disorders:
Elevation of serum potassium
Anorexia, loss of appetite

Johnson syndrome, pemphigus, exacerbation of psoriasis, psoriasiform dermatitis, pemphigoid or lichenoid exanthema or enanthema, alopecia

Decrease in serum sodium, increased elimination of sodium and chlorides and, as a result, water, increased elimination of other electrolytes (esp. potassium, calcium and magnesium), symptomatic electrolyte disorder and metabolic alkalosis, dehydration and hypovolaemia with thirst, transient elevation of creatinine and urea in the blood, elevation of cholesterol and triglycerides in the serum, elevation of uric
**General disorders and administration site conditions:**

- Chest pain, fatigue
- Fever
- Asthenia

**Immune system disorders**

- Anaphylactic or anaphylactoid reactions (such as anaphylactic shock), increase in antinuclear antibodies

**Hepatobiliary disorders**

- Elevation of liver enzymes (incl. transaminases) and/or conjugated bilirubin
- Cholestatic jaundice, liver cell damage

**Reproductive system and breast disorders**

- Transient erectile dysfunction, decreased libido

**Psychiatric disorders**

- Depressive moods, angst, nervousness, unrest, sleep disorders including somnolence
- Confusion
- Attention disorders

### 4.9 Overdose

**Symptoms:**

The symptoms of an overdose of **ACE inhibitors** include excessive dilatation of the peripheral vessels (with marked hypotension, shock), bradycardia, electrolyte disorders and kidney failure. The patient must be monitored very closely.

The clinical signs of an acute or chronic overdose of **furosemide** depend on the extent of the fluid and electrolyte loss. Overdosing can cause hypotension, orthostatic dysregulation and electrolyte disorders (hypokalaemia, hyponatraemia, hypochloraemia) or alkalosis. In the case of stronger fluid losses, marked hypovolaemia, dehydration, circulatory collapse and haemoconcentration with a disposition for thrombosis may occur. Rapid fluid and electrolyte losses can cause delirious conditions. Rarely, anaphylactic shock (symptoms: e.g.
perspiration, nausea, cyanosis, strong drop in blood pressure, disturbed consciousness and even coma) may occur.

**Therapy:**
Therapy is symptomatic and supportive. Helpful measures include primary detoxification (gastric lavage, administration of an absorbent) and measures to restore the haemodynamic balance, such as the administration of alpha1-adrenergic agonists or angiotensin-II (angiotensinamide). Ramiprilate, the active metabolite of ramipril, is hardly dialysable.

In severe cases, the vital parameters must be monitored, and the water and electrolyte balance, the acid-base balance, blood sugar level and urinary excreted substances must be checked regularly and deviations corrected where necessary.