### Core Safety Profile

<table>
<thead>
<tr>
<th>Active substance:</th>
<th>Spirapril</th>
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<tbody>
<tr>
<td>Pharmaceutical form(s)/strength:</td>
<td>Scored tablets, 3mg, 6mg</td>
</tr>
<tr>
<td>P-RMS:</td>
<td>SK/H/PSUR/0008/002</td>
</tr>
<tr>
<td>Date of FAR:</td>
<td>20.12.2011</td>
</tr>
</tbody>
</table>
4 CLINICAL PARTICULARS

4.3 Contraindications

- Known hypersensitivity to spirapril or to any of the excipients.
- In patients with a history of angioedema with or without previous treatment with an
  - angiotensin-converting enzyme inhibitor.
- Pregnancy (see section 4.6 Pregnancy and lactation.)

4.4 Special warnings and precautions for use

Angioedema:
Angioedema of the face, extremities, lips, tongue, glottis, larynx and/or small bowel have been reported in patients treated with angiotensin-converting enzyme inhibitors. The most patients experiencing angioedema complication had been subjected to extended periods of therapy, at daily doses 5 to 10 times the recommended dose. If angioedema occurs, spirapril should be discontinued and the patient observed carefully until swelling disappears. When the tongue, glottis or larynx is involved and airway obstruction is likely, appropriate therapy, e.g. adrenaline solution 1:1000, should be promptly administered.

Impaired renal function: For patients with a creatinine clearance > 30 mL/min, no dose reduction is necessary.

In hypertensive patients with severe renal impairment (creatinine clearance ≤ 30 mL/min) given 6 mg once a day, maximum plasma concentrations of spiraprilat (the pharmacologically active metabolite of spirapril) were often increased by a factor of 2 to 3, but no accumulation after repeated administration has been observed or would be expected. Therefore 3 mg once a day may be appropriate.

Similarly, in congestive heart failure patients with severe renal impairment (creatinine clearance ≤ 30 mL/min), 3 mg may be appropriate for maintenance therapy.

Anaphylactoid reactions during dialysis membrane exposure and desensitization:
Since experience with spirapril is still limited, its use is not recommended. ACE inhibitors should not be used during haemodialysis with high-flux polyacrylonitrile membranes or during LDL-apheresis with dextran sulphate adsorption since, in rare cases, anaphylactoid reactions have been reported. Also, patients undergoing desensitizing treatment with Hymenoptera venom while receiving ACE inhibitors had life-threatening anaphylactoid reactions. These reactions were avoided when ACE inhibitor were temporarily withheld and reappeared upon inadvertent rechallenge.

Impaired hepatic function: In this group of patients, plasma concentrations of spiraprilat may be reduced by about 30%; however, no dose adjustment is necessary.
**Use in the elderly:** Based on the clinical and pharmacokinetic data in the elderly (> 65 years of age), no dose adjustment is necessary.

**Use in children:** Since no experience with spirapril in children is available, its use cannot be recommended.

**Symptomatic hypotension:** Hypotension has been seen rarely in patients with hypertension or congestive heart failure but may be, especially following the first dose, a possible consequence of the use of spirapril in salt-/volume-depleted patients, e.g. those treated with diuretics. In such patients, the diuretic treatment should preferably be interrupted for 2 to 3 days prior to initiation of spirapril therapy and resumed thereafter. If diuretic treatment cannot be interrupted, spirapril should be initiated under medical supervision. If hypotension occurs, the patient should be placed in a supine position and, if necessary, be given an i.v. infusion of normal saline. A transient hypotensive response is not a contraindication for further use, and subsequent doses can usually be given without difficulty once blood pressure has been normalised.

**Hyperkalaemia:** Risk factors for the development of hyperkalaemia in association with ACE inhibitors include renal insufficiency and diabetes mellitus. Therefore spirapril should be used cautiously in such conditions. The use of spirapril with potassium supplements or potassium-sparing diuretics may lead to a significant increase in serum potassium. If concomitant use of these agents is indicated because of hypokalaemia, they should be used with caution and under strict monitoring of serum potassium concentrations.

**Renovascular hypertension:** As a consequence of its inhibition of the renin-angiotensin-aldosterone system, spirapril may cause changes in renal function in patients with renovascular hypertension. Especially in hypertensive patients with unilateral or bilateral renal artery stenosis, administration of spirapril may cause increases in blood urea nitrogen and serum creatinine. In such patients, renal function should be closely monitored during therapy.

In some patients with no apparent pre-existing renal vascular disease increases in blood urea nitrogen and serum creatinine may rarely develop. These increases are usually small and transient and are more likely to occur in patients with pre-existing renal impairment.

**Use during surgery/anaesthesia:** In patients undergoing major surgery or anaesthesia with agents that produce hypotension, spirapril may block angiotensin II formation secondary to compensatory renin release. Should hypotension occur, it can be corrected by volume expansion, if it is considered to be due to this mechanism.

**Neutropenia/agranulocytosis:** There is no evidence that long-term treatment with spirapril causes any adverse effects on haematological parameters. Periodic monitoring of white blood cell counts in patients with autoimmune diseases should be considered, since on rare occasions, blood dyscrasia has been reported with other ACE inhibitors particularly in this group of patients.
**Cough**: Persistent non-productive cough has been reported with ACE inhibitors, presumably due to inhibited degradation of endogenous bradykinin. This cough always resolves after discontinuation of therapy. ACE-inhibitor-induced cough must be considered in the differential diagnosis of cough.

**Aortic or mitral stenosis**: As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis.

**Other**: The product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 **Interaction with other medicinal products and other forms of interaction**

**Anticipated interactions resulting in concomitant use not being recommended**

**Dipeptidyl peptidase-IV inhibitors**: The risk of angioedema may be increased in patients receiving co-administration of ACE inhibitors and dipeptidyl peptidase-IV inhibitors (e.g. vildagliptin).

**Medicinal products causing leucopenia**: There may be increased risk of leucopenia with the combination use of spirapril and immunosuppressants, cytotoxic drugs or allopurinol.

**Anticipated interactions to be considered**

**Other antihypertensive drugs**: spirapril can increase the blood-pressure lowering effect of other antihypertensives such as beta-blockers, calcium channel blockers and direct renin inhibitors. Patients on diuretics may occasionally experience an excessive reduction in blood pressure after initiation of therapy with spirapril (see section 4.4 Special warnings and precautions for use).

**Lithium**: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

**Antidiabetics**: In rare cases, diabetic patients receiving an ACE inhibitor concomitantly with insulin or oral antidiabetics may develop hypoglycaemia. Such patients should therefore be advised about the possibility of hypoglycaemic reactions, and should be monitored accordingly.
**Gold:** Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy.

**Alcohol, barbiturates, nitrates, narcotics or antidepressants:** Concomitant administration of spirapril with alcohol, barbiturates, nitrates, narcotics, or antidepressants may potentiate orthostatic hypotension.

**Non-steroidal anti-inflammatory drugs (NSAIDs):** Concomitant administration of certain non-steroidal anti-inflammatory drugs (e.g. indomethacin) including COX-2 inhibitors may weaken antihypertensive activity of spirapril. The combination of these drugs and ACE inhibitors (including spirapril) can increase the risk of renal impairment and hyperkalaemia. Therefore, monitoring of renal function and potassium level is recommended specially in patients with volume depletion.

**Probenecid:** Concomitant use of probenecid may enhance the pharmacodynamic response of ACE inhibitors including spirapril.

**Erythropoietin:** Patient responsiveness to erythropoietin may decrease when use concomitantly with ACE inhibitors.

**Absence of interaction**

Ingestion of spirapril with a high-fat meal has no significant effect on the bioavailability of spirapril, but may delay its absorption by approximately one hour.

The effect of diclofenac, glibenclamide, hydrochlorothiazide, nicardipine or cimetidine on plasma concentrations of spirapril and spiraprilat is negligible; concomitant administration of spirapril with rifampicin results in a 20 to 30 % lower plasma concentration of spiraprilat; however, these changes do not necessitate a dose adjustment when spirapril is used in combination with the above drugs.

Spirapril does not alter the pharmacokinetics of digoxin or the anticoagulant effect (prothrombin time) of warfarin.

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**

Animal data provide no evidence that spirapril has any embryotoxic or teratogenic potential. However, ACE inhibitors can cause fetal and neonatal morbidity and death when given to pregnant women. Several dozen cases have been reported in the world literature. Exposure to ACE inhibitors during the second and third trimesters of pregnancy is known to induce human foetotoxicity, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios, presumably due to impaired fetal renal function, has also been reported; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these were due to ACE inhibitor
exposure. In addition, use of ACE inhibitors during the first trimester of pregnancy has been associated with a potentially increased risk of birth defects. Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded (See section 5.3.).

When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started. Monitoring of the fetal development should be performed on a regular basis. In women planning to become pregnant, ACE inhibitors (including spirapril) should not be used. Women of child-bearing age should be made aware of the potential risk and ACE inhibitors (including spirapril) should only be given after careful counseling and consideration of individual risks and benefits. Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

**Lactation**

It is not known whether spirapril passes into human milk. Therefore, patients on spirapril should not breast-feed. Because no information is available regarding the use of spirapril during breastfeeding, spirapril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

**Fertility**

At high multiples of the human dose (2,500 times), spirapril did not have any adverse effects on fertility in rats.

### 4.7 Effects on ability to drive and use machines

As with other antihypertensive drugs, it is advisable to exercise caution when driving or operating machines.

### 4.8 Undesirable effects

Adverse reactions are ranked under heading of frequency, using the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$), not known (cannot be estimated from the available data).

- **Nervous system disorders**
  Not known: Headache, dizziness

- **Ear and labyrinth disorders**
  Not known: Vertigo*
• **Vascular disorders**
  Not known: Hypotension (see **Use in salt-/volume-depleted patients** in section 4.4 Special warnings and precautions for use).

• **Respiratory, thoracic and mediastinal disorders**
  Not known: Upper respiratory irritation (including cough)

• **Gastrointestinal disorders**
  Not known: Abdominal discomfort, Diarrhoea*

• **Skin and subcutaneous tissue disorders**
  Not known: Rash

  Not known: Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, larynx and/or small bowel have been reported in patients treated with angiotensin-converting enzyme inhibitors®.

• **General disorders and administration site conditions**
  Not known: Fatigue

* These symptoms were reported in patients with congestive heart failure

Class effects: Adverse events reported for other ACE inhibitors (class-effects) may also occur in patients receiving spirapril: photosensitivity, hyperkalaemia, nausea, vomiting, and erectile dysfunction. Angioedema and neutropenia/agranulocytosis have also been reported (see section 4.4).

### 4.9 Overdose

No cases of acute overdose have as yet been reported; the intake of 10 times the recommended dose may, however, lead to headache and hypotension. Should overdose occur, gastric lavage should be considered, the patient (in particular the cardiovascular system) closely monitored and, if indicated, symptomatic treatment undertaken.