Part VI: Summary of activities in the risk management plan by product

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

| Important identified risks | Arrhythmia  
|                           | Hepatic encephalopathy / insufficiency  
|                           | Hypersensitivity / angioneurotic oedema  
|                           | Renal insufficiency / acute renal failure  
|                           | Teratogenicity  
|                           | Water and electrolyte imbalances including hypo- and hyperkalemia, hyponatremia, hypercalcemia  
|                           | Hypotension  
|                           | Asthenia  
|                           | Bronchospasm  
| Important potential risks | Neutropenia / agranulocytosis  
|                           | Use during lactation  
|                           | Pancreatitis  
|                           | Thrombocytopenia  
|                           | Anemia (aplastic and hemolytic)  
|                           | Steven-Johnson syndrome  
| Important missing information | Use in children and young people  

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan (if applicable)

Not applicable

VI.1.3 Summary of Post authorisation efficacy development plan (if applicable)

Not applicable

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Overall, approximately 20% of the world’s adults are estimated to have hypertension, when hypertension is defined as BP in excess of 140/90 mm Hg. The prevalence dramatically increases in patients older than 60 years: in many countries, 50% of individuals in this age group have hypertension. Worldwide, approximately 1 billion people have hypertension, contributing to more than 7.1 million deaths per year. National health surveys in various countries have shown a high prevalence of poor control of hypertension. These studies have reported that prevalence of hypertension is 22% in Canada, of which 16% is controlled; it is 26.3% in Egypt, of which 8% is controlled; and it is 13.6% in China, of which 3% is controlled.

VI.2.2 Summary of treatment benefits

For the treatment of (essential) hypertension a wide variety of medication is available. Choice of treatment may depend on disease severity, co-morbidities, concomitant medication, ethnicity etc.
The use of Angiotensin-converting enzyme (ACE) inhibitors alone or in combination with (thiazide) diuretics is one of the treatment options for hypertension. Other treatment options are angiotensin II antagonists, calcium channel blockers, beta-blockers, alpha-blockers, either as monotherapy or sometimes in combination. The components of perindopril/indapamide have shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone.

**VI.2.3 Unknowns relating to treatment benefits**

The efficacy and tolerability of perindopril in children and young people, alone or in combination, have not been established.

**VI.2.4 Summary of safety concerns**

**Important identified risks**

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
<th>Preventability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>Hyperkalaemia can induce serious and sometimes fatal arrhythmia. Hypokalaemia increase the cardiac toxicity of cardia glycosides and the risk of arrhythmias.</td>
<td>Close patient monitoring and according tests should be performed.</td>
</tr>
<tr>
<td>Hepatic encephalopathy / insufficiency</td>
<td>Use during hepatic encephalopathy and severe hepatic insufficiency is contraindicated.</td>
<td>The use of medicine should be discontinued and appropriate medical supervision implemented</td>
</tr>
<tr>
<td>Hypersensitivity / angioneurotic oedema</td>
<td>Angioneurotic oedema may occur at any time during treatment. Some patients may experience life-threatening anaphylactic reactions.</td>
<td>If such occurs, treatment should be stopped immediately and suitable monitoring of the patient should be initiated.</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>The combination of perindopril and indapamide does not prevent the onset of hypokalaemia, particularly in diabetic patients or in patients with renal insufficiency.</td>
<td>As with any antihypertensive agent containing a diuretic, regular monitoring of plasma potassium should be carried out.</td>
</tr>
<tr>
<td>Renal insufficiency /acute renal failure</td>
<td>In the case of severe renal insufficiency, treatment is contraindicated.</td>
<td>Careful patient monitoring should be performed.</td>
</tr>
<tr>
<td>Teratogenicity</td>
<td>The use of ACE inhibitors is not recommended during the first trimester of pregnancy. The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy.</td>
<td>Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.</td>
</tr>
<tr>
<td>Hypotension</td>
<td>There is a risk of sudden hypotension in the presence of pre-existing sodium depletion (in particular in individuals with renal artery stenosis).</td>
<td>The patient should therefore be tested systematically for clinical signs of fluid and salt depletion, which may occur with an intercurrent episode of diarrhoea or vomiting.</td>
</tr>
</tbody>
</table>
Water and electrolyte imbalances including hypo- and hyperkalemia, hyponatraemia, hypercalcemia.

Disturbances in the electrolyte- and fluid imbalance, especially hypo- or hyperkalaemia, hyponatraemia and hypercalcemia may occur.

The levels of the electrolytes should be monitored. In severe cases the administration of the medicine should be discontinued.

### Asthenia

This is a common event associated with the use of this product.

Standard monitoring for signs/symptoms

### Bronchospasm

This is an uncommon event associated with the use of this product.

Standard monitoring for signs/symptoms

### Important potential risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known (Including reason why it is considered a potential risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia / agranulocytosis</td>
<td>Neutropaenia/agranulocytosis, thrombocytopenia and anaemia have been observed in patients receiving treatment with ACE inhibitors. Neutropenia occurs only rarely in patients with normal renal function and without other complications. Perindopril should be used with extreme caution in patients with collagen vascular disease, on immunosuppressant therapy or treatment with allopurinol or procainamide, or who have a combination of these complicating factors, especially if there is pre-existing impaired renal function. If perindopril is used in this patient group, ongoing monitoring of white blood cell counts is recommended and patients should be instructed to report any sign of infection (e.g. sore throat, fever).</td>
</tr>
</tbody>
</table>

### Use during lactation

Perindopril tert-butylamine/ Indapamide is contraindicated during lactation. Because no information is available regarding the use of perindopril tert-butylamine during breastfeeding, Perindopril tert-butylamine/ Indapamide is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant. Indapamide is excreted into human breast milk. Indapamide is closely related to thiazide diuretics, which have been linked to the reduction or cessation of milk secretion in lactating women. Hypersensitivity to sulphonamide derivatives, hypokalaemia and kernicterus may arise.

As both drugs can induce serious adverse reactions for the breastfed child, it should be determined whether breastfeeding should be stopped or the drug withdrawn after an assessment of how important the treatment is for the mother.

### Pancreatitis

This undesirable effect may be observed during the treatment and the frequency of appearance is very rare (< 1/10000).

### Thrombocytopenia

Thrombocytopenia has been reported with ACE inhibitors, including in neonates after exposure near term.

### Anaemia (aplastic and hemolytic)

Anaemia has been reported with ACE inhibitors in specific circumstances (patients who have had a kidney transplant, patients undergoing haemodialysis)

### Steven Johnson syndrome

Steven Johnson is a very rare event.

### Important missing information
<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use in children and young people</td>
<td>This medicine should not be given to children and young people as the efficacy and tolerability of perindopril in children and young people, alone or in combination, have not been established.</td>
</tr>
</tbody>
</table>

**VI.2.5 Summary of additional risk minimisation measures by safety concern**

Not applicable

**VI.2.6 Planned post authorisation development plan (if applicable)**

Not applicable

**VI.2.7 Summary of changes to the risk management plan over time**

Not applicable, since this is the first RMP for this product.