## VI.2 Elements for a public summary

### VI.2.1 Overview of disease epidemiology

**Hyperaldosteronism** (excessive levels of hormone-aldosterone)**:**

Hyperaldosteronism is a disorder in which the adrenal gland (small gland on top of kidney) releases too much of aldosterone into the blood. Aldosterone is a hormone which regulates the salt and water balance of the body. Primary hyperaldosteronism is due to a problem of the adrenal glands (most cases due to non-cancerous tumour of gland) themselves and secondary hyperaldosteronism, could be as a result of a problem elsewhere in the body like in genes, diet, or a medical disorder such as with the heart, liver, kidneys, or high blood pressure.

Data on adults suggest that hyperaldosteronism has a female preponderance. Equivalent information is not available for children, in whom primary hyperaldosteronism is likely to represent a greater proportion of cases. The literature on adults demonstrates that blacks are at significantly greater risk for high blood pressure-related morbidity and mortality than whites are. The prognosis of primary hyperaldosteronism is good with early diagnosis and treatment. The prognosis of secondary hyperaldosteronism depends on the cause of the condition.

**Hypertension (High blood pressure):**

Blood pressure is a measurement of the force against the walls of the arteries as heart pumps blood through body. Hypertension is another term used to describe high blood pressure. Hypertension affects about 1 billion people around the world. According to a new report published by the European Commission, the occurrence of hypertension varied considerably by country. Countries in East Central Europe, particularly Bulgaria, Romania, and Slovakia, and the Mediterranean area (particularly Greece) reported the highest proportion (≥ 50%) of people under long-term treatment for hypertension, whereas in Belgium, The Netherlands, and Luxembourg (Benelux), hypertension was mentioned by ≤ 25%.The risk factors for getting high blood pressure includes obesity, smoking, too much alcohol, stress, diabetes (high sugar level in body) and family history of high blood pressure. High blood pressure increases chance of having a stroke, heart attack, heart failure, kidney disease, or early death.

**Nephrotic syndrome:**

Nephrotic syndrome is a group of symptoms that include protein in the urine, low blood protein levels, high cholesterol levels and swelling. Nephrotic syndrome is caused by different disorders that damage the kidneys. Nephrotic syndrome can affect all age groups. In children, it is most common between ages 2 and 6 and it occurs slightly more often in males than females. Some people may eventually need dialysis and a kidney transplant. Because diabetes is major cause of nephrotic syndrome, American Indians, Hispanics, and African Americans have a higher incidence of nephrotic syndrome than do white persons. The outcome varies. The condition may be acute (short-term) or chronic (long term) and not respond to treatment. The complications that occur can also affect the outcome.

**Liver cirrhosis:**

Cirrhosis is scarring of the liver and poor liver function. It is the last stage of liver damage. Viral infection and excessive alcohol use are the common causes for this damage. Available data suggest that about 0.1% of the European population is affected by cirrhosis. There are, however, large intra-European variations. About 0.1% of Hungarian males will die of cirrhosis every year compared with 0.001% of Greek females. The liver cannot heal or return to normal function once damage is severe. Cirrhosis can lead to serious complications.

**Heart Failure and Oedema (swelling)**:

Heart failure is a condition in which the heart is no longer able to pump out enough oxygen-rich blood. Heart failure is often a long-term (chronic) condition, but it may come on suddenly. The weakening of the heart's pumping ability causes fluid and blood back up into lung and accumulation of fluid into various parts of body (oedema).It can be caused by many different heart problems. The incidence and the prevalence of heart failure increase sharply with increasing age. Estimates calculated within the last decade suggest a prevalence of ~1–2% in the overall population and >10% in the elderly population. It has been estimated that there are currently 6.5 million chronic heart failure patients in Europe and 5 million in the USA, and these numbers are increasing because of the ageing of the global population. Often, heart failure can be controlled by taking medicine, changing lifestyle, and treating the condition that caused it. Most of the time, heart failure is a chronic illness that gets worse over time. Some people develop severe heart failure. Medicines, other treatments, and surgery no longer help at this stage. People with heart failure may be at risk for dangerous heart rhythms.

**Malignant ascites:**

Ascites is an abnormal build up of fluid in the abdomen**.** It occurs when the body makes more fluid then it can remove. Ascites can occur with cancer and other conditions. When ascites due to cancer, or if the fluid in the abdomen contains cancer cells, it is often called malignant ascites. Ascites develops most often with ovarian, uterine (endometrial), cervical, colorectal, stomach (gastric), pancreatic or primary liver cancers. Cancer that spreads to the liver can also cause ascites. Symptoms of ascites can vary depending on their cause and other factors. Symptoms of ascites include: swelling of abdomen, feeling of bloating, fatigue, nausea, vomiting, indigestion, loss of appetite, ankle or leg swelling etc. One retrospective review of causes of malignant ascites found that ovarian cancer had the highest proportion of patients who developed ascites at 37.7%, followed by pancreaticobiliary cancers (21%), gastric cancer (18.3%), esophageal cancer (4.0%), colorectal cancer (3.7%), and breast cancer (3.0%).

### VI.2.2 Summary of treatment benefits

Spironolactone may be prescribed for the treatment of accumulation of fluid in the tissues as a result of heart disorders, especially in cases which are difficult to treat; raised blood pressure with the salt-free diet and medicine which increase urine production (diuretics), if the effect of these alone is inadequate; certain kidney disorders, if the effect of diuretics is inadequate or if these cannot be used because potassium levels in the blood are too low; accumulation of fluid in the tissues in the abdominal cavity. Spironolactone may also be used during medical investigations (diagnostics) to confirm the presence of disorders in which too high a level of aldosterone is produced in the adrenal gland (known as Conn's disease) and treatment before an operation and in patients with Conn's disease who do not undergo surgery or in whom surgery is impossible.

Accord has not conducted any studies for Spironolactone on expected benefit considering its similarity to the currently marketed product.

### VI.2.3 Unknowns relating to treatment benefits

The effectiveness of spironolactone has not been established in the following patient's groups: paediatric patients (age ≤18 yrs) and pregnant or breast feeding women.

### VI.2.4 Summary of safety concerns

**Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| Increased levels of potassium in blood (Hyperkalaemia) | Do not take Spironolactone Accord if patient has hyperkalaemia (raised blood potassium levels) or other conditions associated with hyperkalaemia.<br>If patient is on certain medications like potassium-sparing diuretic (including eplerenone) or potassium-supplements, or dual-RAAS blockade with the combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB).<br>Take special care with Spironolactone Accord:<br>• If patient has severe renal dysfunction which is being | Do not use Spironolactone Accord if there is too much potassium (hyperkalaemia) in blood.<br>Take special care with Spironolactone Accord if patient has severe renal dysfunction which is being simultaneously treated with potassium supplements<br>Use of certain diuretics, called potassium-sparing diuretics (such as amiloride and triamterene); concomitant use with Spironolactone Accord should be avoided.<br>If you need to use this medicine for a long time, your doctor should performed perform regular follow-up |

| Risk | What is known | Preventability |
|---|---|---|
| | simultaneously treated with potassium supplements, since sever raised blood potassium level can occur which can result in sudden, unexpected stopping of heart (sometimes fatal).<br><br>If patient uses certain diuretics, called potassium-sparing diuretics (such as amiloride and triamterene); concomitant use with Spironolactone Accord should be avoided, because the risk of excessively high levels of potassium in the blood (hyperkalaemia) is increased. Possible Side Effects:<br><br>The most common side effects are hyperkalaemia<br><br>Metabolism and nutrition disorders<br><br>Very common: too much potassium in the blood (hyperkalaemia) in patients with severe renal dysfunction who are receiving concomitant treatment with potassium supplements (see also "Take special care with | checks to check levels of potassium and sodium in your blood<br><br>Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, your doctor may wish to alter your dose of Spironolactone Accord if you are taking any of the following.<br><br>• medicines for high blood pressure including ACE inhibitors, ganglion-blocking drugs<br><br>• other diuretics<br><br>• non-steroidal anti-inflammatory drug (NSAID) such as aspirin or ibuprofen<br><br>• potassium supplements<br><br>• heparin or low molecular weight heparin (medicines used to prevent blood clots) |

| Risk | What is known | Preventability |
|---|---|---|
| | Spironolactone Accord")<br><br>Common: too much potassium in the blood (hyperkalaemia) in (1) patients with severe renal dysfunction, (2) patients receiving treatment with ACE inhibitors or potassium chloride, (3) the elderly, and (4) diabetic patients<br><br>Nervous system disorders: Rare: loss of ability to move the lower half of the body due to higher blood potassium level | • antipyrine<br>• noradrenaline<br>• barbiturates or narcotics<br>• medicines known to cause hyperkalaemia (raised blood potassium levels)<br>• Cholestyramine<br><br>Corticosteroids, ACTH |
| Important identified risk: Poor function of the kidneys (Renal insufficiency) | Do not take Spironolactone if you suffer from severely impaired kidney function or from a sudden or rapidly deteriorating kidney disease, including cases in which no urine, or very little urine, is being produced.<br><br>Take special care with Spironolactone if you are elderly: in elderly patients it is recommended to start at the lowest possible dose and to increase it gradually until the desired effect has been obtained. Caution and regular medical | Do not use Spironolactone and tell your doctor if this warning apply to you, or has done so in the past.<br><br>If you have a kidney disorder; your doctor should exercise caution when treating you.<br><br>Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, your doctor may wish to alter your dose of |

| Risk | What is known | Preventability |
|---|---|---|
| | checks are advisable, in particular where kidney function is impaired. | Spironolactone Accord if you are taking any of the following.<br>• medicines for high blood pressure including ACE inhibitors, ganglion-blocking drugs<br>• other diuretics<br>• non-steroidal anti-inflammatory drug (NSAID) such as aspirin or ibuprofen<br>• potassium supplements<br>• heparin or low molecular weight heparin (medicines used to prevent blood clots)<br>• antipyrine<br>• noradrenaline<br>• barbiturates or narcotics<br>• medicines known to cause hyperkalaemia (raised blood potassium levels)<br>• Cholestyramine<br>• Corticosteroids, ACTH |

| **Risk** | **What is known** | **Preventability** |
|---|---|---|
| Hormonal disturbances (gynaecomastia, voice alteration, and impotence) | Spironolactone may induce impotence and menstrual abnormalities, gynaecomastia (enlargement of mammary glands) is commonly seen in male patients receiving spironolactone therapy.<br><br>Reproductive system and breast disorders<br><br>*Very common:* Men: reduced libido, erectile dysfunction, impotence, enlargement of the mammary glands (gynaecomastia);<br><br>Women: breast disorders, tenderness of the breasts, menstrual disorders, deepening of the voice (in many cases irreversible) | Do not use Spironolactone Accord and tell your doctor if you experience any of these side effects.<br><br>In case of long term treatment of young patients with Spironolactone Accord, your doctor should weigh advantages carefully against long- term disadvantages. |
| Serious skin reactions | The patients may experience following serious skin reactions-<br><br>• Itchiness and blistering of the skin around the lips and the rest of the body (Stevens-Johnson syndrome)<br><br>• Detachment of the top layer of skin from the lower layers | Do not use Spironolactone Accord and tell your doctor if you experience any of these side effects. |

| Risk | What is known | Preventability |
|---|---|---|
| | of skin, all over the body (toxic epidermal necrolysis)<br>• Skin rash, fever and swelling (which could be symptoms of something more serious, drug rash and eosinophilia and systemic symptoms)<br>The frequency of these side effects is not known. | |
| Lower white blood cell counts (Agranulocytosis) | The patient may developed rare blood disorders like very severe blood abnormalities (deficiency of white blood cells) accompanied by sudden high fever, severe throat pain and mouth ulcers (agranulocytosis), blood abnormality (platelet deficiency) accompanied by bruises and tendency to bleed (thrombocytopenia). | Do not use Spironolactone Accord and tell your doctor if you develop any of these side effects. |

**Important potential risks**

| Risk | What is known |
|---|---|
| Nil | - |

**Missing information**

| Risk | What is known |
|---|---|
| Use in pregnancy | There are very limited data on the use of spironolactone during pregnancy in humans. Experimental animal studies have shown reproductive toxicity associated with the anti-androgenic effect of spironolactone. Spironolactone should not be used during pregnancy. Metabolites of spironolactone have been detected in breast milk. Spironolactone should not be used during breast feeding. Spironolactone may induce impotence and menstrual irregularities.<br><br>If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. |

### VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

### VI.2.6 Planned post authorisation development plan

No studies planned.

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

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| 4.0 | 27-Oct-2015 | Following safety concerns is added<br><br>Important Identified Risk:<br>• Hormonal disturbances (gynaecomastia, voice alteration, and impotence)<br>• Serious skin reactions<br>• Agranulocytosis | RMP is updated as per Day 50 comments received from Germany (DE), dated 22-Oct-2015.<br>SmPC and PIL have been updated as per Day 50 comments received from Estonia (EE), Spain (ES), Ireland (IE), Sweden (SE) and<br>United Kingdom (UK). |
| 3.0 | 03-Jan-2015 | No changes in safety concerns | RMP has been updated based on revised SmPC. |
| 2.0 | 03-Jun-2014 | **Following safety concern is added**<br><br>Important identified risk:<br>Renal insufficiency<br><br>**Following safety concern has been removed**<br><br>Important potential risk: Risk of tumours secondary to long-term use / high doses | Part VI.2.1 Overview of disease epidemiology and VI.2.2 Summary of treatment benefits<br>have been updated. |