VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Congestive Heart failure and Oedema (swelling):

Heart failure is a condition where the heart is no longer able to pump enough oxygen-rich blood. Heart failure is often a long-term (chronic) condition, but it may come on suddenly and some patients may be severely affected. The weakening of the heart's pumping ability causes fluid and blood to back up into the lungs and accumulation of fluid into various parts of body (oedema). The number of cases of heart failure increase sharply with increasing age. Estimates calculated within the last decade suggest about ~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 an ageing population. Heart failure can often be controlled by taking medicine, changing lifestyle, and treating the condition that caused it.

Hepatic cirrhosis with ascites and oedema (Liver cirrhosis):

Cirrhosis is characterised by scarring of the liver and poor liver function and is the last stage of liver damage. Viral infection and excessive alcohol intake are the most common causes of

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cirrhosis. Available data suggest that about 0.1% of the European population is affected by cirrhosis. There are, however, large variations within Europe. 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 its normal function once the damage is severe.

Ascites:

Ascites is an abnormal build-up of fluid in the abdomen. It occurs when the body makes more fluid than it can remove. Ascites can occur with cancer but also with other conditions. When ascites is 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 the cause and other factors but usually include swelling of the abdomen, feeling of bloating, fatigue, nausea, vomiting, indigestion, loss of appetite, ankle or leg swelling etc.

Nephrotic syndrome:

Nephrotic syndrome is a group of symptoms that includes protein in the urine, low blood protein levels, high cholesterol levels and swelling. Nephrotic syndrome is caused by different disorders that damage the kidneys and can affect all age groups. In children, it is most common between the ages two and six and it occurs slightly more often in males than females. Some people may eventually need dialysis and a kidney transplant. Diabetes is major cause of nephrotic syndrome, Nephrotic syndrome occurs more often in American Indians, Hispanics and African Americans than in whites.

Hyperaldosteronism (excessive levels of aldosterone):

Hyperaldosteronism is a disorder in which the adrenal gland (small gland on top of kidney) releases too much 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 and most cases are due to non-cancerous tumours of the adrenal gland. Secondary hyperaldosteronism

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could be a result of a disease elsewhere in the body like in the genes, diet or a medical disorder such as heart, liver or kidneys problems, or high blood pressure.

Data on adults suggest that hyperaldosteronism occur more often in females. Equivalent information is not available for children, in whom primary hyperaldosteronism is likely to represent a greater proportion of cases. 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 the body. Hypertension affects about 1 billion people around the world. According to a new report published by the European Commission, the occurrence of hypertension varies considerably by country. Countries in East Central Europe, particularly Bulgaria, Romania, and Slovakia, and the Mediterranean area (particularly Greece) report the highest proportion (≥ 50%) of people under long-term treatment for hypertension. The proportion in the Benelux countries is reported to be≤ 25%. The risk factors for developing high blood pressure include obesity, smoking, too much alcohol, stress, diabetes (high sugar level in body) and family history of high blood pressure. High blood pressure also increases the chance of having a stroke, heart attack, heart failure, kidney disease, or early death.

VI.2.2 Summary of treatment benefits

Spironolactone is used for the following indications:

- Congestive heart failure
- Nephrotic syndrome - a kidney disorder that causes too much fluid in your body
- Ascites- too much fluid in your abdomen and ‘oedema’ - accumulation of fluid beneath skin or in one or more cavities of the body that produces swelling, for example caused by cirrhosis of the liver
- Primary aldosteronism - extra fluid in your body caused by too much of a hormone called aldosterone

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- Essential hypertension (Spironolactone may be combined with other medicines to control the blood pressure)

Children should only be treated under guidance of a paediatric specialist.

VI.2.3 Unknowns relating to treatment benefits

Not applicable

VI.2.4 Summary of safety concerns

Table 12 Part VI - Summary table of safety concerns

Important identified risks

Risk	What is known	Preventability
High level of potassium in blood (hyperkalaemia)	Excessive potassium in the blood in a very common side effect of spironolactone treatment. Concomitant administration of spironolactone with certain medicines, potassium supplements and food rich in potassium may lead to severe hyperkalaemia (increased potassium blood level). The symptoms of severe hyperkalaemia might include muscle cramps, irregular heart rhythm, diarrhoea, nausea, dizziness or headache.	Yes, by monitoring for early symptoms. Patients should inform the prescriber if they notice any symptoms of hyperkalaemia or if they are taking medicines that reduce the elimination of potassium in the urine (e.g. potassium-sparing diuretics, ACE inhibitors, angiotensin-2-antagonists) or potassium supplements.

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Risk	What is known	Preventability
Renal insufficiency (kidney failure)	Sudden kidney failure has been reported with the use of spironolactone. spironolactone is contraindicated in adult and paediatric patients with acute renal insufficiency, significant renal impairment, anuria (inability to urinate or discharge urine).	Yes, patient should not be administered if patient suffer from severe kidney disease, children with moderate to severe kidney disease and suffer from kidney disease especially children with hypertension.
Hormonal disturbances (gynaecomastia, voice alteration and impotence)	Gynecomastia (breast enlargement in men) is usually reversible when spironolactone is discontinued, but in rare cases breast enlargement may persist. The development of gynecomastia seems to be related to both dose levels and duration of treatment. spironolactone is contraindicated in adult and paediatric patients Addison's disease (a hormone deficiency characterised by extreme weakness, loss of weight and low blood pressure).	Yes, spironolactone should not be administered if patients have a hormone deficiency characterised by extreme weakness, loss of weight and low blood pressure.

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Risk	What is known	Preventability
Drug-drug interactions with digoxin, noradrenaline and antikaliuretic agents	Caution should be exercised in the management of patients subjected to regional or general anaesthesia while they are being treated with spironolactone. Spironolactone has been reported to increase serum digoxin half-life. This may result in increased serum digoxin levels and subsequent digitalis toxicity.	Yes, patients should inform to the doctors if they have treated with anaesthetic or taking drugs like digoxin, noradrenaline and antikaliuretic agents and should be monitored carefully.
Serious skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis)	Itchiness and blistering of the skin around the lips and the rest of the body (Stevens-Johnson syndrome), detachment of the top layer of skin from the lower layers of skin, all over the body (toxic epidermal necrolysis) and skin rash, fever and swelling (which could be symptoms of something more serious, drug rash and eosinophilia and systemic symptoms) have been reported with spironolactone.	Yes, patient should inform doctor immediately if you experience any of the serious skin reactions after taking this medicine.

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Risk	What is known	Preventability
Leukopenia (including agranulocytosis)	Leukopenia including agranulocytosis (lowered white blood cell count) has been reported with spironolactone.	Yes, patient should inform to doctor if they experienced lowered white blood cell count.

Important potential risks

None

Missing information

Risk	What is known
Use during pregnancy and lactation	Spironolactone must not be taken during pregnancy as side effects were observed in young animals in animal trials and the potential risk to humans is not known. Spironolactone, is excreted into human breast milk. Spironolactone should not be used during breast-feeding. Since many actives are excreted into breast milk and the potential risk of adverse effects in infants is unknown and if use of spironolactone is considered essential, an alternative method of infant feeding should be instituted. Patients should inform their doctor if they are planning to have a baby or they think they may be pregnant or breast feeding.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimisation measures. This medicine has no additional risk minimisation measures.

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VI.2.6 Planned post authorisation development plan

No studies planned.

VI.2.7 Summary of changes to the Risk Management Plan over time

RMP version 1.0 has been amended to version 2.0 (current document) to reflect the change in safety concerns for spironolactone, as per the request received from the competent authority (as per day 70 and day 105 preliminary assessment reports). Table below reflects the changes proposed in safety.

Version	Date	Safety concerns	Comment
3.0	02-May-2018	Not applicable, same as previous version 2.0	Updated epidemiology text in line with day 120 draft assessment report spironolactone DK/H/2730/001-003/DC, Applicant: Vale Pharmaceuticals Limited, dated 14-Mar-2018.
2.0	27-Oct-2017	The below safety concerns were added to the important identified risks: • Renal insufficiency • Hormonal disturbances (gynaecomastia, voice alteration and impotence) • Drug-drug interactions with digoxin, noradrenaline and antikaliuretic agents • Serious skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis) • Leukopenia (including agranulocytosis) The below important potential risk was deleted from the list of safety concerns • Electrolyte and hydration disorders	Updated safety concerns, as per the day 70 and 105 preliminary assessment report for spironolactone DK/H/2730/001-003/DC, Applicant: Vale Pharmaceuticals Limited, dated 27-Jan-2017.

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