VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Furosemide is indicated for treatment of oedema (associated with cardiac disease, liver disease, renal disease, pulmonary oedema) and arterial hypertension.

A study in Australia[1] in 2001 revealed that 1.6% of population self-reported having oedema; 1.0% of male population and 2.1% of female population (ABS 2001 National Health Survey, Australia's Health 2004, AIHW).

VI.2.2 Summary of treatment benefits

Taking into account the published information on the use and dosage of furosemide, it can be concluded that the use of this medicinal product in the proposed indication and according to the dosage recommendations given in the SmPC is fully justified. Safety and efficacy of furosemide in treatment of the proposed indications is sufficiently evident from its approved clinical use.

A wide variety of medical conditions can cause edema, including kidney, liver, and heart disease. Several of the body's organs and glands affect fluid balance. Diseases that affect these organs and prevent them from functioning normally can cause the kidneys to retain salt and water (two major components of edema fluid). This excess fluid then "leaks" out of the body's circulatory system and into surrounding tissues, causing them to swell. Pulmonary edema can be a complication of heart failure. Serious, inadequately treated heart failure can result in pulmonary edema. As the heart pumps less efficiently, fluid leaks out of the veins in the lungs and fills the air sacs, making it difficult to breathe. Pulmonary edema is life-threatening, and if left untreated, can rapidly become fatal. People with less severe heart failure that does not lead to pulmonary edema may also experience swelling in their ankles.2

VI.2.3 Unknowns relating to treatment benefits

It is considered that there are no unknowns relating to treatment benefits.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
- Coma and pre-coma hepaticum associated with hepatic encephalopathy (severe liver disorders with loss of or onset of loss of consciousness,	Patients suffering from severe liver disorders with loss of or onset of loss of consciousness, associated with brain damage should not use Furosemid Orifarm as it is a known contraindication.	There is no specific measure to prevent the risk. The risk is mentioned as a contraindication in the summary of Product Characteristics and patient information leaflet. The risk can be reduced by not allowing the product to be used in patients who are at risk of

Risk	What is known	Preventability
associated with brain damage).		severe liver disorders.
- Severe hypokalemia (reduced potassium level in the blood)	Furosemid Orifarm must not be used in case of severely reduced potassium or sodium level in the blood as it is a known contraindication.	There is no specific measure to prevent the risk. The risk is mentioned as a contraindication in the summary of Product Characteristics and patient information leaflet. The risk can be reduced by not allowing the product to be used in patients who are at risk of severe hypokalemia.
- Severe hyponatremia (reduced sodium level in the blood)	Furosemid Orifarm must not be used in case of severely reduced potassium or sodium level in the blood as it is a known contraindication.	There is no specific measure to prevent the risk. The risk is mentioned as a contraindication in the summary of Product Characteristics and patient information leaflet. The risk can be reduced by not allowing the product to be used in patients who are at risk of severe hyponatremia.
- Reduced blood volume (Hypovolaemia) or dehydration	Reduced blood volume or dehydration is a known contraindication and patients with this risk should not use Furosemid Orifarm.	There is no specific measure to prevent the risk. The risk is mentioned as a contraindication in the summary of Product Characteristics and patient information leaflet. The risk can be reduced by not allowing the product to be used in patients who are at risk of hypovolaemia or dehydration.
- Drug-drug interactions e.g. lithium, chloral hydrate and aminoglucosides	<u>Furosemide may have an effect on other medicinal products:</u> Lithium Serum lithium levels may be increased when lithium is given together with furosemide, resulting in increased lithium toxicity. Therefore, it is recommended that lithium levels are carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination. Chloral hydrate	There is no specific measure to prevent the risk. The risk is mentioned as interactions in the summary of Product Characteristics and patient information leaflet.

Risk	What is known	Preventability
	In isolated cases, heat sensation, fit of perspiration, agitation, nausea, rise in blood pressure and increased heart rate (tachycardia) may occur after intravenous administration of furosemide within 24 hours after intake of chloral hydrate. Administration of furosemide together with chloral hydrate is therefore to be avoided. Kidney toxic (nephrotoxic) antibiotics The toxic effects of nephrotoxic antibiotics (e.g. aminoglycosides, cephalosporins, polymyxins) may be increased by administering them together with potent diuretics such as furosemide. Ear toxic (ototoxic) antibiotics Furosemide may increase the ear toxicity (ototoxicity) of aminoglycosides (e.g. kanamycin, gentamicin, tobramycin) and other ear toxic medicinal products. Since this may lead to irreversible damage, these medicinal products must only be used with furosemide if clearly indicated.	
- Ear toxicity (Ototoxitity)	Ear Toxic (ototoxic) antibiotics Furosemide may potentiate the ear toxicity of aminoglycosides (e.g. kanamycin, gentamicin, tobramycin) and other ear toxic medicinal products. Since this may lead to irreversible damage, these medicinal products must only be used with furosemide if clearly indicated. There is a risk of ear toxic effects if cisplatin and furosemide are given together. Ear disorders may be experienced as undesirable effects: Hearing disorders, Tinnitus.	There is no specific measure to prevent the risk. The risk is mentioned as an interaction and undesirable effects in the summary of Product Characteristics and patient information leaflet.
- Increased concentration of blood cells (Haemoconcentration)	Increased concentration of blood cells (Haemoconcentration) as a result of fluid loss can occur as an undesirable effect of furosemide. This side effect occurs quite frequently.	There is no specific measure to prevent the risk. The risk is mentioned as an undesirable effect and in the overdose section in the summary of Product Characteristics and patient information leaflet.

Risk	What is known	Preventability
	Excessive fluid loss may cause pronounced Reduced blood volume, dehydration, circulatory collapse and increase in the proportion of red blood cells relative to the plasma with increased risk for blood clot (thrombosis).	
- Reduced number of blood platelets (Thrombocytopenia)	Reduced number of blood platelets (Thrombocytopenia) is an side effect that occurs infrequently.	There is no specific measure to prevent the risk. The risk is mentioned as an undesirable effect in the summary of Product Characteristics and patient information leaflet.
- Severe allergic reactions (Severe anaphylactic and anaphylactoid reactions)	Severe allergic reactions (anaphylactic and anaphylactoid reactions) such as allergic (anaphylactic shock) may occur as rare undesirable effects.	There is no specific measure to prevent the risk. The risk is mentioned as undesirable effects in the summary of Product Characteristics and patient information leaflet.
- Allergic (Anaphylactic) shock	Allergic (Anaphylactic) shock may occur as a rare undesirable effect. First signs of an allergic shock may be skin reactions like flush or hives (urticarial), agitation, headache, extreme sweating (hyperhidrosis), nausea, bluish discoloration of the skin and mucous membranes caused by a lack of oxygen in the blood (cyanosis). Rarely, an anaphylactic shock (symptoms: extreme sweating (hyperhidrosis), nausea, bluish discoloration of the skin and mucous membranes caused by a lack of oxygen in the blood (cyanosis), severe low blood pressure (hypotension), disturbed consciousness up to coma) may occur.	There is no specific measure to prevent the risk. The risk is mentioned as an undesirable effect and in the overdose section in the summary of Product Characteristics and patient information leaflet.
- Kidney inflammation, affecting the fluid that surround the kidney tubules (Tubolointerstital nephritis)	Kidney inflammation, affecting the fluid that surround the kidney tubules (tubolointerstital nephritis) may occur as a rare undesirable effect.	There is no specific measure to prevent the risk. The risk is mentioned as an undesirable effect in the summary of Product Characteristics and patient information leaflet.

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
- Photosensitivity	Photosensitivity may occur as an uncommon undesirable effect.
- Severely reduced number of blood cells caused by insufficient production (Aplastic anaemia), Severely reduced number of certain white blood cells known as granulocytes (agranulocytosis), Lack of red blood cells caused by increased breakdown (haemolytic anaemia)	Severely reduced number of blood cells caused by insufficient production (Aplastic anaemia), Severely reduced number of certain white blood cells known as granulocytes (agranulocytosis), Lack of red blood cells caused by increased breakdown (haemolytic anaemia) may occur as very rare undesirable effects. [1]Signs for agranulocytosis may be fever and shivering, mucous membrane reactions and sore throat.
- Blood clot which may block a blood vessel (Thrombosis)	Blood clot which may block a blood vessel (Thrombosis) (particularly in elderly patients) may occur as a rare undesirable effect with unknown frequency. Excessive fluid loss may cause pronounced reduced blood volume (hypovolaemia), dehydration, circulatory collapse and increased concentration of blood cells (haemoconcentration) with increased risk for blood clot which may block a blood vessel (Thrombosis).
- Inflammation of the pancreas (Acute pancreatitis)	Inflammation of the pancreas (Acute pancreatitis) may occur as a very rare undesirable effect.
- Reduced bile flow caused by reduced bile production (Interhepatic cholestasis)	Reduced bile flow caused by reduced bile production (Interhepatic cholestasis) may occur as a very rare undesirable effect.
- Increased liver enzymes	Increase of certain liver enzyme levels, known as transaminases may occur as a very rare undesirable effect.
- Kidney (renal) failure	Kidney (renal) failure with insufficient urine production and not responding to furosemide is a known contraindication. Certain non-steroidal anti -inflammatory agents, NSAIDS, (e.g. indometacin, acetylsalicylic acid) may reduce the action of furosemide and may cause acute renal failure in cases of pre-existing reduced blood volume (hypovolaemia) or dehydration. Blood-pressure-lowering agents The dosage of cardiac glycosides, diuretics, anti-hypertensive agents, or other drugs with blood-pressure-lowering potential may require adjustment when given together with furosemide as a more pronounced fall in blood pressure may occur. A severe fall in blood pressure with shock in extreme cases and deterioration in renal function (acute renal failure in isolated cases) have been observed especially when medicines called ACE inhibitors or angiotensin II

Risk	What is known (Including reason why it is considered a potential risk)
	receptor antagonists were administered together with furosemide for the first time or at higher doses. The dose of furosemide should be reduced for at least three days, or stopped, before initiating the ACE inhibitor or angiotensin II receptor antagonist or increasing their dose. Renal failure may occur as an undesirable effect of unknown frequency.

VI.2.5 Summary of risk minimisation measures by safety concern

Routine Pharmacovigilance is used for the safety concerns, which are all listed in the SmPC.

There are no specific risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Furosemid Orifarm can be found in Annex 2.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

None.

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

Not applicable as this is the initial risk management plan.