

**VI.2 Elements for a public summary****VI.2.1 Overview of disease epidemiology****Pulmonary edema (Edema of lung/respiratory tract)**

Pulmonary edema occurs in about 1% to 2% of the general population. Between the ages of 40 and 75 years, males are affected more than females. After the age of 75 years, males and females are affected equally. The incidence of pulmonary edema increases with age and may affect about 10% of the population over the age of 75 years. Risk Factors include Exposure to inhaled toxins, aspirated toxins, substances that exerting an effect upon the caliber of blood vessels (histamines, kinins), dense smoke, and the abuse of certain drugs such as cocaine or heroin may increase an individual's risk of pulmonary edema. Young healthy, athletic males may be at increased risk for negative-pressure of edema of lung/respiratory track. The outcome of pulmonary edema depends largely on the underlying cause. Untreated, pulmonary edema can lead to respiratory arrest and death.

**Cirrhosis (Abnormal liver condition)**

Abnormal liver condition in which there is irreversible scarring of the liver (Cirrhosis) is a cause of morbidity and mortality. In the UK, mortality from cirrhosis rose from 6 per 100,000 populations in 1993 to 12.7 per 100,000 in 2000. The majority of the cases of liver disease are accounted for by liver inflammation due to a viral infection, alcoholic liver disease, and nonalcoholic fatty liver disease (build-up of excess fat in the liver cells) (NAFLD). Hepatitis C-related cirrhosis is the most common indication for liver transplantation and accounts for 40% of deaths from liver disease. In fact, hepatocellular carcinoma accounts for 50% to 70% of liver-related mortality. The prevalence of nonalcoholic fatty liver disease and nonalcoholic fatty liver disease (build-up of excess fat in the liver cells) (steatohepatitis) has increased in parallel with the increased epidemics of obesity.

**CHF (Congestive Heart Failure): (Heart's function as a pump is inadequate to meet the body's needs)**

In developed countries, about 1–2% of the general population have CHF. Prevalence rises sharply with age and is more common in men than in women at all ages. Epidemiological studies in the Netherlands suggest a prevalence of CHF of 3.9% in the general population. A survey in, USA reported the prevalence of 2.2% in residents aged 45 years or above. A study in Scotland reported definite LV systolic dysfunction in 2.9% of men and women aged 25–74 years, half of whom had symptoms compatible with CHF. UK population-based study reported a survival of 70% at six months from the time of diagnosis, 62% at 12 months and 57% by 18 months. Many CHF patients are elderly and may suffer from other chronic medical conditions, including lung disease, diabetes, degenerative arthritis or degenerative joint disease or osteoarthritis (group of mechanical abnormalities involving degradation of joints), or dementia.

**Oliguria (Less urine)**

The frequency of oliguria widely varies depending on the clinical setting. In adults, the incidence is about 1% at admission, 2-5% during hospitalization, and 4-15% after cardiopulmonary bypass. Oliguric acute kidney injury occurs in approximately 10% of newborn intensive care unit (ICU) patients. The incidence in children undergoing cardiac surgery is as high as 10-30%. Oliguria affects people of all ages. It is more common in neonatal and older age groups because of comorbid conditions and is more common in early childhood because of the high incidence of illnesses that lead to dehydration. Mortality rates in oliguric acute kidney injury widely vary according to the underlying cause and associated medical condition. It ranges from 5% for patients with community-acquired kidney injury failure to 80% among patients with multi-organ failure in the ICU.

**VI.2.2 Summary of treatment benefits**

A study compared the efficacy of a continuous infusion of high dose furosemide versus a single bolus injection of an equal dose in 20 patients with severe heart failure. The patients received an

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equal dosage, either as a single intravenous bolus injection or as an 8-h continuous infusion preceded by a loading dose. Mean daily urinary volume and sodium excretion were significantly higher after treatment with continuous infusion than with bolus injection, despite significantly lower urinary furosemide excretion. It can be concluded that in patients with severe heart failure, high dose furosemide administered as a continuous infusion is more efficacious than bolus injection.

Accord has not done any studies to evaluate the expected benefits of Accord’s Furosemide considering its similarity to the currently marketed/reference product.

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

Not applicable

**VI.2.4 Summary of safety concerns**

**Important identified risks:**

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
Imbalance of certain ionized salts (Electrolyte disturbances)	Like all medicines, this medicine can cause side effects, although not everybody gets them.  Common (may affect up to 1 in 10 people):  Furosemide can cause an excessive depletion of bodily fluids (e.g. passing urine more often than normal) and minerals (sodium, potassium, magnesium, calcium).  Symptoms that can occur are thirst,	Yes  If you get any side effects, talk to your doctor or pharmacist immediately.

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
	<p>headache, confusion, muscle cramps, increased irritability of the muscles, muscular weakness, heart rhythm disturbances and gastrointestinal problems such as sensation of unease and discomfort in stomach with an urge to vomit, or diarrhoea.</p> <p>If you have a shortage of sodium (sodium deficiency):</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> cramp in the calf muscles</li> <li><input type="checkbox"/> loss of appetite</li> <li><input type="checkbox"/> listlessness</li> <li><input type="checkbox"/> feeling of weakness</li> <li><input type="checkbox"/> dizziness</li> <li><input type="checkbox"/> drowsiness</li> <li><input type="checkbox"/> confusion</li> </ul> <p>If you have a shortage of potassium (potassium deficiency):</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> muscular weakness and the inability to contract one or more muscles (paralysis)</li> <li><input type="checkbox"/> increased excretion of urine</li> <li><input type="checkbox"/> heart problems</li> <li><input type="checkbox"/> in the case of severe potassium</li> </ul>	

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
	<p>deficiency: interference with the function of the intestine or confusion, which can result in coma.</p> <p>If you have a shortage of magnesium and calcium (magnesium and calcium deficiency):</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> increased irritability of the muscles</li> <li><input type="checkbox"/> heart rhythm disturbances.</li> <li><input type="checkbox"/> Lowering of blood pressure, resulting in impaired concentration and reactions, light-headedness, a feeling of pressure in the head, headache, dizziness, drowsiness, a feeling of weakness, visual disturbances, dry mouth and an inability to stand upright</li> </ul>	
<p>Renal dysfunction/insufficiency /renal impairment (Impaired renal function)</p>	<p>Do not take furosemide or ask to your doctor if you have kidney failure or kidney problems.</p> <p>Like all medicines, this medicine can cause side effects, although not everybody gets them.</p> <p>Rare (may affect up to 1 in 1,000 people):</p>	<p>Yes</p> <p>Tell your doctor or pharmacist before taking furosemide injection.</p> <p>If any of the mentioned side effects are observed please inform your doctor immediately.</p>

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
	<p>Acute kidney failure</p> <p>Inflammation of the kidneys associated with blood in the urine, fever and pain in the sides</p> <p>In Children: The doctor will decide on the dosage, depending on how severely the kidneys are affected and on the response to initial doses.</p>	
<p>Drug interactions, in particular with NSAIDs</p>	<p>Non-steroidal anti-inflammatory drugs (NSAIDs) - used for pain and inflammation such as aspirin, ibuprofen, ketoprofen or indometacin can increase the chance of side effects when taken with Furosemide injection.</p>	<p>Yes</p> <p>Tell your doctor or pharmacist before taking furosemide injection.</p>
<p>Digitalis toxicity (Digitalis intoxication)</p>	<p>Digoxin used for heart problems can increase the chance of side effects when taken with Furosemide Injection.</p> <p>Do not use Furosemide Injection if you are taking digoxin, used to treat heart problems.</p>	<p>Yes</p> <p>Tell your doctor or pharmacist before taking furosemide injection.</p>
<p>A disease in which crystals of uric acid deposit in and around</p>	<p>Tell your doctor or pharmacist before taking Furosemide Injection if you have gout.</p>	<p>Yes</p> <p>Tell your doctor or pharmacist before taking</p>

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
<p>joints, causing pain and arthritis (Gout)</p>	<p>Like all medicines, this medicine can cause side effects, although not everybody gets them.</p> <p>joint pain</p> <p>As like other drugs that cause increase in urination (diuretics), furosemide also increase uric acid levels in blood which cause pain and arthritis (gout)</p> <p>If this drug is taken with ciclosporin it may cause crystals of uric acid deposit in and around joints, causing pain and arthritis (gout)</p> <p>If this drug is taken in high dose it may cause pain and arthritis due to accumulation of uric acid in blood (gout).</p>	<p>furosemide if you have gout.</p> <p>Before starting furosemide, tell your doctor if you are taking ciclosporin or other medicine that affect body's defence mechanism (immunomodulators).</p> <p>During the treatment with furosemide, doctor should monitor uric acid level in patient's blood</p>
<p>Blood cell disorders (Blood dyscrasias)</p>	<p>This medicine cause uncommon side effect such as abnormal blood count accompanied by bruising and a tendency to bleed, fluid depletion and thickening of the blood (particular in elderly patients). This may affect up to 1 in 100 people.</p> <p>This medicine cause rare side effects</p>	<p>Yes</p> <p>Before starting the treatment patient should inform to doctor for having any blood disorders.</p> <p>If you observed any side effect associated with blood please inform your doctor</p>

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
	such as abnormal blood count (white blood cell deficiency) accompanied by an increased susceptibility to infection and increase in certain substances (eosinophilic cells) in the blood. This may affect up to 1 in 1000 people.	immediately.
Liver damage	This drug very rarely cause certain liver function disorders and increase in certain liver enzyme which may affect up to 1 in 10,000 people	Yes  If you have severe liver problems (cirrhosis), please talk to your doctor before taking Furosemide injection.
unusual reaction of a drug to particular or individual (Idiosyncratic reaction)	There may some rare side effect occur to specific person which may not associated with drug property.	Yes  Please talk to your doctor if you experience any unusual side effect during the treatment.

**Important potential risks**

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
Diabetes mellitus	Furosemide may decrease the activity of diabetes medicine.  Blood sugar level for diabetic patient	Tell your doctor or pharmacist before taking furosemide if you have

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
	can be increase with furosemide.	diabetes.  Doctor should closely monitor the patient’s blood sugar during the treatment with furosemide.
Hypotension	If you have a shortage of magnesium and calcium (magnesium and calcium deficiency) there may be lowering of blood pressure, resulting in impaired concentration and reactions, light-headedness, a feeling of pressure in the head, headache, dizziness, drowsiness, a feeling of weakness, visual disturbances, dry mouth and an inability to stand upright.  Furosemide along with alcohol may reduce patient’s blood pressure.	Tell your doctor or pharmacist before taking furosemide if you have low blood pressure.  Patient should avoid alcohol during the treatment with furosemide.
Drug interaction with Antihypertensives	The following medicines can affect the way furosemide Injection 10 mg/ml work and increase the chance of you getting side effects:  Medicines used to treat high blood pressure such as ramipril, enalapril, perindopril (called ‘ACE inhibitors’)	Yes  Tell your doctor or pharmacist if you are taking, have recently taken or might take any r medicines for blood pressure control.

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
	<p>or losartan, candesartan, irbesartan (called ‘angiotensin II receptor antagonists’). Your doctor may need to change the dose of your medicine or ask you to stop taking them.</p> <p>Medicines for high blood pressure or heart problems such as aliskiren or hydralazine. Your doctor may need to change the dose of your medicine.</p> <p>Medicines used to treat high blood pressure or prostate problems known as alpha-blockers, such as prazosin and medicines used to treat high blood pressure and other medicines used to remove water from the body known as diuretics, such as amiloride, spironolactone, acetazolamide and metolazone.</p>	
<p>Congenital disorder in the heart (Risk of patent ductus arteriosus in infants)</p>	<p>If furosemide is administered to a baby that was born too early during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.</p>	<p>Yes</p> <p>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.</p>

<b>Risk</b>	<b>What is known</b>	<b>Preventability</b>
Risk of nephrocalcinosis/kidney stones in premature infants	In a baby that was born too early furosemide can be precipitated as nephrocalcinosis/ kidney stones	Yes  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.
Concomitant use with risperidone	The following medicines can affect the way furosemide injection works and increase the chance of getting side effects:  Medicines used for mental problems called ‘psychoses’, such as risperidone.	Yes  Inform the doctor or pharmacist before taking furosemide injection in case the patient, particularly elder patient, is taking risperidone.

**Missing information:**

Nil	
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**VI.2.5 Summary of additional 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 minimising 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**

<b>Version</b>	<b>Date</b>	<b>Safety Concern</b>	<b>Comment</b>
2.0	07 Oct 2014	<p>Following safety concerns are added:</p> <p><b>Important identified risks:</b></p> <ul style="list-style-type: none"> <li>• Gout</li> <li>• Blood dyscrasias</li> <li>• Liver damage</li> <li>• Idiosyncratic reactions</li> </ul> <p>Drug interaction with NSAIDs was re-titled as Drug interactions, in particular with NSAIDs</p> <p><b>Important potential risk:</b> Risk of nephrocalcinosis/ kidney stones in infants was re-termed as risk of nephrocalcinosis/ kidney</p>	<p>Safety concerns and Part VI.2.2 “Summary of treatment benefits” have been updated as per comments given in Type II Preliminary Variation Assessment Report for Furosemide Injection 10 mg/ml Solution for Injection (IE/H/186/001/II/005) dated 03 Sep 2014.</p>

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		stones in premature infants.	