Public Assessment Report

Decentralised Procedure

FUROSEMIDE 10 MG/ML ORAL SOLUTION

Procedure No: UK/H/4074/001/DC

UK Licence No: PL 35574/0001

ALAPIS S.A
LAY SUMMARY

On 21 April 2011, Bulgaria, Cyprus, Greece, Malta, Romania and the UK agreed to grant a Marketing Authorisation to Alapis S.A for the medicinal product Furosemide 10mg/ml Oral Solution (PL 35574/0001; UK/H/4074/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 17 May 2011.

This product is a prescription-only medicine (POM) used to remove the levels of excess water in the body caused by heart, lung, kidney, liver or blood vessel problems.

Furosemide 10mg/ml Oral Solution contains the active ingredient furosemide. Furosemide belongs to a group of medicines called diuretics or water tablets.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Furosemide 10mg/ml Oral Solution outweigh the risks, hence a Marketing Authorisation has been granted.
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## Module 1

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<th><strong>Product Name</strong></th>
<th>Furosemide 10 mg/ml Oral Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Furosemide</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>10 mg/ml oral solution</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>10 mg/ml</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Alapis S.A., 2, Aftokratoros Nikolaou str. 17671, Athens, Greece</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>Bulgaria, Cyprus, Greece, Malta and Romania.</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/4074/001/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 17 May 2011</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Furosemide 10 mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1 ml of solution contains 10 mg of Furosemide.

Each 1 ml of solution also contains 98.5 mg Ethanol and 350 mg Sorbitol

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Oral Solution

Clear solution with a characteristic orange odor.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Furosemide is indicated in all conditions requiring prompt diuresis in patients who are unable to take solid dose forms. Indications include cardiac, pulmonary, hepatic and renal oedema, peripheral oedema due to mechanical obstruction or venous insufficiency and hypertension.

4.2 Posology and method of administration
This liquid should only be taken orally.

The medication should be administered in the morning to avoid nocturnal diuresis.

Adults (more than 18 years of age): The usual initial daily dose is 40mg. This may be adjusted until an effective dose is achieved.

Elderly: in the elderly, Furosemide is generally eliminated more slowly. Dosage should be titrated until the required response is achieved.

This product is not recommended to use in children below 18 years of age.

4.3 Contraindications
Hypovolaemia or dehydration. Anuria. Renal failure with anuria not responding to furosemide, or as a result of poisoning by nephrotoxic or hepatotoxic agents, or associated with hepatic coma. Severe hyperkalaemia, hyperkalaemia and severe hyponatraemia. Pre-comatose and comatose states associated with hepatic encephalopathy. Breast feeding.

Contra-indicated in hypersensitivity to Furosemide, sulphonamides or any of the excipients listed. Patients allergic to sulphonamides may show cross-sensitivity to furosemide.

4.4 Special warnings and precautions for use
This product should not be given to children because its ethanol content may affect their CNS.

Caution is required in patients liable to electrolyte deficiency. Regular monitoring of serum sodium, potassium and creatinine is generally recommended during furosemide therapy; particularly close monitoring is required in patients at high risk of developing electrolyte imbalances or in case of significant additional fluid loss. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of furosemide. Where indicated, steps should be taken to correct hypotension or hypovolaemia before commencing therapy.

Urinary output must be secured. Patients with partial obstructions of urinary outflow for example patients with prostatic hypertrophy or impairment of micturition have an increased risk of developing acute urinary retention and require careful monitoring.

Particularly careful monitoring is necessary in:
• Patients with hypotension
• Patients who are at risk from a pronounced fall in blood pressure
• Patients with gout
• Patients with hepatorenal syndrome
- Patients with hypoproteinaemia, e.g. associated with nephrotic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated). Cautious dose titration is required
- Patients that might manifest latent diabetes
- Diabetic patients who might show increased insulin requirements
- Premature infants (possible development nephrocalcinosus/nephrolithiasis; renal function must be monitored and renal ultrasonography performed).

The use of some diuretics is considered to be unsafe in acute porphyria therefore caution should be exercised.

**Excipient Warnings**

This product contains:

**Ethanol (alcohol)** 11.7 vol %, i.e. up to 369.6mg per dose, equivalent to 9.4 ml beer, 3.9 ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, epilepsy.

**Sorbitol**

It may cause flatulence, abdominal distension or diarrhoea if given in large quantities to adults who are unable to take solid oral dose forms of furosemide.

Patients with rare hereditary problems of fructose intolerance, should not take this medicine.

4.5 **Interaction with other medicinal products and other forms of interaction**

**ACE Inhibitors:** Enhanced hypotensive effect when given with diuretics. A marked fall in blood pressure and deterioration in renal function may be seen when ACE inhibitors are added to furosemide therapy. The dose of furosemide should be reduced for at least three days, or the drug stopped, before initiating the ACE inhibitor or increasing the dose of an ACE inhibitor.

**Alpha-blockers:** Enhanced hypotensive effect when diuretics are given with alpha-blockers, also increased risk of first dose hypotension with post-synaptic alpha-blockers such as prazosin.

**Analgesics:** Diuretics can increase the risk of nephrotoxicity of NSAIDs, also antagonism of diuretic effect. Antagonism of diuretic effect (especially with indomethacin and ketorolac). Salicylic toxicity may be increased by furosemide.

**Angiotensin –II Receptor Antagonists:** Enhanced hypotensive effect when diuretics given with angiotensin-II receptor antagonists.

**Anti-arrhythmics:** Hypokalaemia caused by loop diuretics increases cardiac toxicity with amiodarone, disopyramide, flecainide, and antagonises the action of lidocaine and mexiletine.

**Antibacterials:** Avoid the use of diuretics in lymecycline treatment. There is an increased risk of ototoxicity when loop diuretics are given with aminoglycosides, polymyxins or vancomycin. Since this may lead to irreversible damage, these drugs must only be used with furosemide if there are compelling medical reasons. Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.

**Antidepressants:** Possible increase of hypokalaemia when loop diuretics are given with reboxetine. There is an enhanced hypotensive effect when diuretics are given with MAOIs. There is an increased risk of postural hypotension when diuretics are given with tricyclic antidepressants.

**Antiepileptics:** There is an increased risk of hyponatraemia when diuretics are given with carbamazepine. The effects of furosemide are antagonised by phenytoin.

**Antifungals:** There is an increased risk of hypokalaemia when loop diuretics are given with amphotericin.

**Antipsychotics:** Hypokalaemia caused by diuretics increase the risk of ventricular arrhythmias with amisulpiride or sertindole. An enhanced hypotensive effect may be seen when diuretics are given with phenothiazines. Hypokalaemia caused by diuretics increases risk of ventricular arrhythmias with pimozide (avoid concomitant use).

**Antivirals:** Plasma concentration of diuretics may be increased by nelfinavir, ritonavir or saquinavir.
**Atomoxetine:** Hypokalaemia caused by diuretics increases the risk of ventricular arrhythmias with atomoxetine.

**Barbiturates:** Plasma concentrations of diuretics may be decreased. There may be an increased risk of osteomalacia when diuretics are taken in combination with Phenobarbital.

**Beta-blockers:** There is an enhanced hypotensive effect when diuretics are given with beta-blockers. Hypokalaemia caused by loop diuretics increases the risk of ventricular arrhythmias with sotalol.

**Cardiac glycosides:** Hypokalaemia caused by loop diuretics increases cardiac toxicity with cardiac glycosides.

**Ciclosporin:** There is an increased risk of nephrotoxicity and possibly hypermagnesaemia when diuretics are given with ciclosporin.

**Cisplatin:** There is a risk of increased ototoxic effects if cisplatin and furosemide are given concomitantly. In addition, nephrotoxicity of cisplatin may be enhanced if furosemide is not given in low doses (e.g. 40mg in patients with normal renal function) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

**Corticosteroids:** The diuretic effect of diuretics is antagonized by corticosteroids. There is an increased risk of hypokalaemia when loop diuretics are given with corticosteroids.

**Other Diuretics:** There is an increased risk of hypokalaemia when loop diuretics are given with acetazolamide. Profound diuresis is possible when metolazone is given with furosemide. There is an increased risk of hypokalaemia when loop diuretics are given with thiazides and related diuretics.

**Lithium:** Loop diuretics reduce the excretion of lithium, which may lead to increased plasma concentrations and a risk of toxicity. Therefore, it is recommended that lithium levels are carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination.

**Potassium salts:** There is an increased risk of hypokalaemia when given with potassium salts.

**Sucralfate:** Furosemide and sucralfate must not be taken within 2 hours of each other as sucralfate decreases the absorption of furosemide from the intestine and so reduces its effect.

**Sympathomimetics, Beta:** There is an increased risk of hypokalaemia when loop diuretics are given with high doses of beta<sub>2</sub>sympathomimetics.

**Tacrolimus:** There is an increased risk of hypokalaemia when given with tacrolimus.

**Theophylline:** There is an increased risk of hypokalaemia when loop diuretics are given with theophylline.

**Carbenoxolone, prolonged use of laxatives, liquorice:** May increase the risk of developing hypokalaemia.

**Warfarin and clofibrate:** Warfarin and clofibrate compete with furosemide in the binding to serum albumin. This may have clinical significance in patients with low serum albumin levels (e.g. in nephrotic syndrome). Furosemide does not change the pharmacokinetics of warfarin to a significant extent, but a strong diuresis with associated dehydration may weaken the antithrombotic effect of warfarin.

Probenecid, methotrexate and other drugs which, like furosemide, undergo significant renal tubular secretion may reduce the effect of furosemide. Conversely, furosemide may decrease renal elimination of these drugs. In case of high-dose treatment (in particular, of both furosemide and the other drugs), this may lead to increased serum levels and an increased risk of adverse effects due to furosemide or the concomitant medication.

### 4.6 Pregnancy and lactation

**Pregnancy:**
Results of animal work, in general, show no hazardous effect of furosemide in pregnancy. There is clinical evidence of safety of the drug in the third trimester of human pregnancy; however, furosemide
crosses the placental barrier. It must not be given during pregnancy unless there are compelling medical reasons.

**Lactation:**
Furosemide passes into breast milk and may inhibit lactation. Breastfeeding must be avoided during treatment with furosemide.

4.7 **Effects on ability to drive and use machines**
Mental alertness may be reduced and the ability to drive or operate machinery may be impaired.

4.8 **Undesirable effects**
The frequencies of adverse events are ranked according to the following:
Very common ($\geq 1/10$),
Common ($\geq 1/100$ to $<1/10$),
Uncommon ($\geq 1/1,000$ to $<1/100$),
Rare ($\geq 1/10,000$ to $<1/1,000$),
Very rare ($<1/10,000$),
Not known (cannot be estimated from the available data)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common ($\geq 1/10$)</th>
<th>Common ($\geq 1/100$ to $&lt;1/10$)</th>
<th>Uncommon ($\geq 1/1,000$ to $&lt;1/100$)</th>
<th>Rare ($\geq 1/10,000$ to $&lt;1/1,000$)</th>
<th>Very rare ($&lt;1/10,000$)</th>
<th>Not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
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<td>bone marrow depression, (necessitates withdrawal of treatment), leucopenia, eosinophilia</td>
<td>agranulocytosis, aplastic anaemia, haemolytic anaemia</td>
<td>thrombocytopenia</td>
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<tr>
<td>Cardiac disorders</td>
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<td>Cardiac arrhythmias</td>
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<tr>
<td>Congenital, familial and genetic disorders</td>
<td>Patien ductus arteriosus</td>
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<td>Ear and labyrinth disorders</td>
<td>Tinnitus, reversible or irreversible loss of hearing (although usually transitory, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephritic syndrome) and/or when intravenous furosemide has been given too rapidly)</td>
<td></td>
<td>Tinnitus, reversible or irreversible loss of hearing (although usually transitory, particularly in patients with renal failure, hypoprotein aemia (e.g. in nephritic syndrome) and/or when intravenous furosemide has been given too rapidly)</td>
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<tr>
<td>Eye disorders</td>
<td>visual disturbance</td>
<td>Acute Pancreatitis</td>
<td>Acute Pancreatitis</td>
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<td>Gastrointestinal disorders</td>
<td>dry mouth, thirst, nausea, bowel motility disturbances, vomiting, diarrhea, constipation</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>Malaise, Fever</td>
<td>Malaise, Fever</td>
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<tr>
<td>Hepato-biliary disorders</td>
<td>Pure Intrahepatic Cholestasis, Hepatic function abnormal, Jaundice</td>
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<tr>
<td>Investigations</td>
<td>creatinine increased, blood urea increased</td>
<td>Transaminases increased, blood</td>
<td>Transaminases increased, blood</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>dehydration, hyponatraemia, pre-existing hypochloremic metabolic alkalosis may be aggravated, hypokalaemia, hypocalcaemia, hypomagnesemia (incidences of the last three are reduced by triamterene)</td>
<td>impaired glucose tolerance (by hypokalaemia), hyperuricaemia, gout, reduction of serum HDL-cholesterol, elevation of serum LDL-cholesterol, elevation of serum triglycerides, metabolic acidosis</td>
<td>tetany</td>
<td></td>
<td></td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>muscle cramps, muscle weakness</td>
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<tr>
<td>Nervous system disorders</td>
<td>Paraesthesia, confusion</td>
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<tr>
<td>Psychiatric disorder</td>
<td>Psychiatric disorder NOC</td>
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</tbody>
</table>

(Incidence rapidly)
<table>
<thead>
<tr>
<th>Renal and urinary disorders</th>
<th>Reduced diuresis, urinary incontinence, urinary obstruction (in patients with hyperplasia of the prostate, bladder inability to empty, urethral stricture unspecified)</th>
<th>nephrocalcinosis (in pre-term infants treated with Furosemide), interstitial nephritis, acute renal failure</th>
<th>nephrocalcinosis (in pre-term infants treated with Furosemide), interstitial nephritis, acute renal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Rash, photosensitivity</td>
<td>Rash, photosensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urticaria, purpura, erythema multiforme, exfoliative dermatitis, itching, bullous lesions</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>decreased blood pressure, (which, if pronounced may cause signs and symptoms such as impairment of concentration and reactions, light-headedness, sensations of pressure in the head, headache, dizziness, drowsiness, weakness, disorders of vision, dry mouth, orthostatic intolerance)</td>
<td>decreased blood pressure, (which, if pronounced may cause signs and symptoms such as impairment of concentration and reactions, light-headedness, sensations of pressure in the head, headache, dizziness, drowsiness, weakness, disorders of vision, dry mouth, orthostatic intolerance)</td>
<td>Hypotension, hypovolaemia</td>
</tr>
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<td></td>
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<td></td>
<td>Vasculitis, Thrombosis, shock</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Vasculitis, Thrombosis, shock</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Severe anaphylactic or anaphylactoid reactions</td>
</tr>
</tbody>
</table>

Premature infants
If furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus. Risk of nephrocalcinosis/nephrolithiasis (see Tetany and reduced serum calcium and section 4.4)
4.9 Overdose
Overdosing may lead to dehydration and electrolyte depletion through excessive diuresis. Severe potassium loss may lead to serious cardiac arrhythmias. Treatment of overdose consists of fluid replacement and electrolyte imbalance correction. No specific antidote to furosemide is known. If ingestion has only just taken place, attempts may be made to limit further systemic absorption of the active ingredient by measures such as gastric lavage or those designated to reduce absorption (e.g. activated charcoal).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group:
High-Ceiling Diuretic Sulfonamide - CO3C A 01
Furosemide is a potent loop diuretic which inhibits sodium and chloride reabsorption at the Loop of Henlé. The drug eliminates both positive and negative free water production. Furosemide acts at the luminal face of the epithelial cells by inhibiting co-transport mechanisms for the entry of sodium and chloride. Furosemide gains access to its site of action by being transported through the secretory pathway for organic acids in the proximal tubule. It reduces the renal excretion of uric acid. Furosemide causes an increased loss of potassium in the urine and also increases the excretion of ammonia by the kidney.

5.2 Pharmacokinetic properties
Furosemide is a weak carboxylic acid which exists mainly in the dissociated form in the gastrointestinal tract. Furosemide is rapidly but incompletely absorbed (60-70%) on oral administration and its effect is largely over within four hours. The optimal absorption site is the upper duodenum at pH 5.0. Regardless of route of administration, 69-97% of activity from a radio-labelled dose is excreted in the first 4 hours after the drug is given. Furosemide is mainly eliminated via the kidneys (80-90%); a small fraction of the dose undergoes biliary elimination and 10-15% of the activity can be recovered from the faeces.

When oral doses of Furosemide are given to normal subjects the mean bioavailability of the drug is approximately 52% but the range is wide. In plasma, Furosemide is extensively bound to proteins mainly to albumin. The unbound fraction in plasma averages 2 - 4% at therapeutic concentrations. The volume of distribution ranges between 170 - 270ml/Kg. The half life of the β phase ranges from 45 - 60 min. The total plasma clearance is about 200ml/min. Renal excretion of unchanged drug and elimination by metabolism plus faecal excretion contribute almost equally to the total plasma clearance. Furosemide is in part cleared by the kidneys in the form of the glucuronide conjugate.

5.3 Preclinical safety data
There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Liquid sorbitol
Glycerol
Sodium dihydrogen phosphate dihydrate
Ethanol (96%)
Orange flavor
Sodium hydroxide (32% w/v)
Purified water.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
30 months
3 months after opening

6.4 Special precautions for storage
Store in the original package in order to protect from light.
6.5 Nature and contents of container
Amber (Type III) glass bottle, with child-resistant, tamper-evident cap with PEBD seal, along with a 5 ml metered syringe with 0.1 ml graduation.

Capacity: 150 ml

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Alapis S.A.
2, Aftokratoros Nikolaou str.
17671, Athens, Greece

8 MARKETING AUTHORISATION NUMBER(S)
PL 35574/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/05/2011

10 DATE OF REVISION OF THE TEXT
17/05/2011
Module 3

PACKAGING LEAFLET: INFORMATION FOR THE USER
Furosemide 10mg/ml Oral Solution

Furosemide

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed only for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of these side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

1. WHAT Furosemide IS AND WHAT IT IS USED FOR

The name of your medicine is Furosemide 10mg/ml Oral Solution (referred to as Furosemide in this leaflet). The active ingredient in your medicine is furosemide. Furosemide belongs to a group of medicines called diuretics, or water tablets. Furosemide can be used to reduce the levels of excess water in the body caused by heart, lung, kidney, liver or blood vessel problems.

2. BEFORE YOU TAKE Furosemide

Do not take Furosemide and tell your doctor if you:

- Are allergic (hypersensitive) to Furosemide, sulphonamides or any other ingredients in this liquid (listed in Section 6). The signs of an allergic reaction include a rash, itching or swelling of the face, lips, mouth or throat. This could be a sign of having too little water in the body.
- Have diabetes.
- Have been told by your doctor you have low blood volume. Signs of low blood volume can include your skin turning pale, feeling dizzy, faint or nauseous and feeling very thirsty.
- Are passing water (urine) at all or only a small amount each day.
- Have kidney failure or liver problems.
- Have a severe change in blood salts, such as high potassium levels, very low potassium levels or very low sodium levels. You may notice signs of this such as muscle cramps, weakness and tiredness.
- Are allergic to sulfonamides (a group of antibiotics called sulfonamides). Are pregnant, breastfeeding (see section Pregnancy and Breast-feeding). Patients in a coma should not be given this medicine.

3. HOW TO TAKE Furosemide

Follow your doctor's instructions and those given on this leaflet. The recommended dose is 10 mg per 10ml (1/10th of a cup) in the morning. This medicine is usually taken on an empty stomach. This medicine can cause your blood pressure to fall more than usual, particularly if you have an enlarged prostate gland. If you have an enlarged prostate gland:

- Avoid sudden changes in activity, especially when you get out of bed at night. You may feel dizzy.
- Have regular check-ups with your doctor to check the effectiveness of the medicine.
- Take special care with Furosemide.

4. IF YOU TAKE TOO MUCH Furosemide

If you take too much Furosemide, contact your doctor or pharmacist.

5. POSSIBLE SIDE EFFECTS

The most common side effects (which may affect more than 1 in 10 people)

- Sudden change in blood salts such as high potassium levels, very low potassium levels or very low sodium levels. You may notice signs of this such as muscle cramps, weakness and tiredness.
- Allergic reactions (see section Pregnancy and Breast-feeding).

The following side effects may occur:

- Feeling dizzy.
- Diarrhoea.
- Headache.
- Fluid loss in the mouth and throat.
- Feeling hot and flushed.
- Nasal irritation.
- Fever.
- Rash.
- Loss of appetite.
- Tiredness or weakness.
- Swelling in the legs, ankles or feet.
- Clearing of the head.
- Skin sensations.
- Numbness of the hands and feet.
- Sore throat.
- Cough.
- Earache.
- Chest pain.
- Blurred vision.
- Coughing up blood or sputum.
- Changes in hearing.
- Changes in sight.
- Heartburn or indigestion.
- Constipation.
- Diarrhoea.
- Abdominal pain.
- Nervousness.
- Loss of appetite.
- Rash.
- Swelling in the body.
- Dizziness.
- Tiredness.
- Headache.
- Numbness or burning sensation in the arms or legs.
- Feeling cold.
- Irregular heartbeat.
- Unusual tiredness or weakness.
- Shortness of breath.
- Muscle pain.
- Nausea.
- Vomiting.
- Abdominal pain.
- Increased thirst.
- Incontinence.
- Drowsiness.
- Dizziness.
- Headache.
- Nausea.
- Vomiting.
- Abdominal pain.
- Increased thirst.
- Incontinence.
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PAR Furosemide 10 mg/ml Oral Solution

UK/H4074/001/DC

This medicine contains alcohol (ethanol). The daily dose of 40 mg Furosemide would include 32 mg alcohol, equivalent to 10 mL of beer (5%) and 4.2 mL of wine (12%).

If you are pregnant or breast-feeding - you have liver disease - you have epilepsy - you have had a brain injury or brain disease - you are going to give this medicine to a child.

This medicine also contains soya lecithin (1428). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine product.

May have a mild laxative effect. Calorie free, 2.8 kcal/3.3 kJ.

A HOW TO TAKE Furosemide

Always take this medicine as your doctor or pharmacist has told you. Look on the label and ask the doctor or pharmacist if you are not sure. Always take this medicine in the evening. It is best to take your dose in the morning.

Taking this medicine
- This medicine contains 10 mg of furosemide in each mL.
- Take this medicine by mouth.
- Swallow your tablet or capsule whole.

Older People
If you are an older person, your doctor may start you on a lower dose and gradually raise this dose.

If you take more Furosemide than you should
If you take more of the medicine than you should, tell a doctor or go to a hospital straight away. Take the medicine pack with you so they know what you have taken.

If you forget to take Furosemide
If you forget a dose, take it as soon as you remember it. However, if it is nearly time for the next dose, do not take missed dose. Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Furosemide can cause side effects, although not everybody gets them.

An allergic reaction may include:
- any kind of skin rash
- difficulty in breathing, fever and collapse
- more painful allergic reactions including swelling of the kidneys and blood vessels and particular sensitivity of the skin to sunlight and other sources of light.

If you get any of the following side effects, see your doctor as soon as possible:
- changes in the amounts of water, salt or minerals in your body. The signs of this you may feel are thirst, headache, feeling dizzy particularly when standing up, feeling confused, muscle twitches and unusual heart beats. These may happen suddenly but also over time. If you have any problems you may be at risk of these symptoms.
- difficulty in passing water (urine)
- a change in the amount of blood cells. The signs you may feel are feeling weak, unexplained breathlessness or blushing, getting more infections and some skin problems such as rash, itching and a serious illness with blurring of the skin, mouth, eyes and genitalia.
- swelling of the pancreas. This may show as severe pains in the back and ribs in the area in and around the stomach (the abdomen) and jaundice which shows as yellowing of the skin and the whites of the eyes caused by liver or blood problems.
- tingling or numbness in the hands and feet.
- sudden severe joint pains linked to increased amounts of uric acid in the blood.
- blood clots forming when you are severely dehydrated.
- low blood pressure. The signs you may feel are feeling unwell and/or concentration, feeling light-headed, a feeling of pressure in the head, headache, feeling dizzy, feeling weak, changes in vision, dry mouth and feeling cold when standing up.

This medicine may raise cholesterol and lipid (fat) levels in the blood.

If this medicine is used in babies born too soon (prematurely), this medicine can cause:
- persistence of a blood channel that normally closes in or around birth. This may cause heart failure, failure to grow, Steven's Johnson, weakness of the heart and rapid pulse.

Soy protein and/or calcium deposits in the body.

Tell your doctor if you get any of these side effects:
- feeling sick, vomiting, generally feeling unwell.
- any side effects not listed in this leaflet, tell your doctor or pharmacist.

5. HOW TO STORE Furosemide

Keep out of the reach of children.

Store in the original package in order to protect from light.

After you have opened the bottle, this medicine expires after 3 months. Take this medicine back to the pharmacy three months after you last open.
Module 4
Labelling

Carton:
It also contains ethanol and sorbitol. See leaflet for further information. Read the package leaflet before use. Oral use. Keep out of the reach and sight of children. Store in the original package in order to protect from light. This medicine should be disposed of 3 months after first opening.

**Marketing Authorisation Holder:**
Alapis S.A.
2, Aftokratoros Nikolaou str.
17671, Athens, Greece
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Furosemide 10mg/ml Oral Solution (PL 35574/0001; UK/H/4074/001/DC) could be approved. This application was submitted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Bulgaria, Cyprus, Greece, Malta and Romania as Concerned Member States (CMS).

The product is a prescription-only medicine (POM) indicated in all conditions requiring prompt diuresis in patients who are unable to take solid dose forms. Indications include cardiac, pulmonary, hepatic and renal oedema, peripheral oedema due to mechanical obstruction or venous insufficiency and hypertension.

This is an application made according to Article 10.1 of 2001/83/EC, as amended, claiming to be a generic medicinal product of the reference product Lasix 10mg/ml Liquid (Hoechst Marion Roussel Limited, UK). The originator product is Lasilix 10mg/ml oral solution, which was originally granted a licence to Sanofi-Aventis, France on 20 October 1987.

Furosemide is a potent loop diuretic which inhibits sodium and chloride reabsorption at the Loop of Henlé. The drug eliminates both positive and negative free water production. Furosemide acts at the luminal face of the epithelial cells by inhibiting co-transport mechanisms for the entry of sodium and chloride. Furosemide gains access to its site of action by being transported through the secretory pathway for organic acids in the proximal tubule. It reduces the renal excretion of uric acid. Furosemide causes an increased loss of potassium in the urine and also increases the excretion of ammonia by the kidney.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved with the end of procedure (Day 210) on 21 April 2011. After a subsequent national phase, the licence was granted in the UK on 17 May 2011.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Furosemide 10 mg/ml Oral Solution |
| Name(s) of the active substance(s) (INN) | Furosemide |
| Pharmacotherapeutic classification (ATC code) | Sulfonamides, plain (C03C A01) |
| Pharmaceutical form and strength(s) | 10 mg/ml oral solution |
| Reference numbers for the Decentralised procedure | UK/H/4074/001/DC |
| Reference Member State (RMS) | United Kingdom |
| Concerned Member States (CMS) | Bulgaria, Cyprus, Greece, Malta and Romania |
| Marketing Authorisation Number(s) | PL 35574/0001 |
| Name and address of the authorisation holder | Alapis S.A., 2, Aftokratoros Nikolaou str. 17671, Athens, Greece |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Furosemide
Chemical name: 5-(aminosulphonyl)-4-chloro-2-(2-furanyl methyl)amino benzoic acid,
4-Chloro-N-furfuryl-5-sulphamoyl anthranilic acid.
4-Chloro-2[(furan-2-methyl)amino]-5-sulphamoyl benzoic acid

Structure:

![Structure](image)

Molecular formula: C_{12}H_{11}ClN_{2}O_{5}S
Molecular mass: 330.7
Appearance: Furosemide is a white or almost white crystalline powder which is
practically insoluble in water, acetone, sparingly soluble in alcohol and
practically insoluble in methylene chloride. It dissolves in solutions of
alkali hydroxide.

Furosemide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance furosemide are covered by
a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients liquid sorbitol, glycerol, sodium
dihydrogen phosphate dihydrate, ethanol (96%), orange flavour, sodium hydroxide (32% w/v)
and purified water.

All excipients comply with their respective European Pharmacopoeia monograph with the
exception of the orange flavour and sodium hydroxide which are compliant with suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all
excipients.

None of the excipients contain materials of animal or human origin. No genetically modified
organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate a product that could be
considered a generic medicinal product of the reference product Lasilix 10mg/ml oral
solution (Sanofi-Aventis, France).

Details of the pharmaceutical development of the product have been supplied and are
satisfactory.

Comparative impurity profiles have been provided for the proposed and originator products.
Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated using pilot batches and has shown satisfactory results. The applicant has committed to performing process validation with the first three full-scale batches of the drug product.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
The finished product is packaged in Type III amber glass bottles with a child-resistant, tamper-evident cap with PEBD seal together with a 5 ml metered syringe with 0.1 ml graduation and is available in pack sizes of 150 ml.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 30 months for the unopened product, which reduces to 3 months once opened, with the storage conditions ‘Store in the original package in order to protect from light’.

Bioequivalence/bioavailability
No bioequivalence studies have been submitted and none are required to support an application of this type.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The leaflet conforms to the requirements. The test shows that the patients/users are able to act upon the information that the leaflet contains.

MAA form
The MAA form is satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical viewpoint.
III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of furosemide are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment. As this product is intended for generic substitution with a currently marketed brand leader, i.e. no increase in environmental burden is anticipated, the justification is accepted.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Pharmacokinetics
In accordance with Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), a bioequivalence study is not requested if the product is an aqueous solution at time of administration and contains an active substance in the same concentration as an approved oral solution. No bioequivalence study has been submitted with this application and none is required.

Efficacy
No new efficacy data were submitted and none were required for this application.

Safety
No new safety data were submitted and none were required for this application

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the SmPC and in-line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for this application.

Conclusion
There are no objections to the approval of this application from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Furosemide 10mg/ml Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none were required for an application of this type.

EFFICACY
No new efficacy data were submitted and none were required for an application of this type.

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with furosemide is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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