SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Frusol 50mg/5ml Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains 50 milligrams Furosemide

Excipient(s) with known effect:

Ethanol	397.28mg/5ml
Liquid Maltitol (E 965)	2.5g/5ml
Propylene Glycol (E1520)	0.35mg/5ml

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

A clear, colourless to straw coloured liquid (Oral Solution)

4.1. Therapeutic indications

Furosemide is indicated in all conditions requiring prompt diuresis, including cardiac, pulmonary, hepatic and renal oedema, peripheral oedema due to mechanical obstruction or venous insufficiency and hypertension.

It is also indicated for the maintenance therapy of mild oedema of any origin.

4.2. Posology and method of administration

Posology

Adults

The usual initial daily dose is 40mg. This may be adjusted until an effective dose is achieved.

Paediatric population

1 to 3mg/Kg body weight daily up to a maximum total dose of 40mg/day.

Elderly

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

Method of administration

For oral use.

Suitable for administration via nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes. For further instructions see section 6.6.

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

4.3. Contraindications

Contra-indicated conditions	**See also**
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or sulphonamides, sulphonamide derivatives.	
Hypovolaemia and dehydration (with or without accompanying hypotension)	Section 4.4
Severe hypokalaemia: severe hyponatraemia	Section 4.4
Comatose or pre-comatose states associated with hepatic cirrhosis or encephalopathy	Section 4.4
Anuria or renal failure with anuria not responding to furosemide, renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents	
Impaired renal function with a creatinine clearance below 30ml/min per 1.73 m2 body surface area	Section 4.4
Addison's disease	Section 4.4
Digitalis intoxication	Section 4.5
Concomitant potassium supplements or potassium sparing diuretics	Section 4.5
Breast-feeding women	Section 4.6

4.4. Special warnings and precautions for use

Conditions requiring correction before furosemide is started (see also section 4.3)

- Hypotension
- Hypovolaemia
- Severe electrolyte disturbances – particularly hypokalaemia, hyponatraemia and acid-base disturbances

Furosemide is not recommended

- In patients at high risk for radiocontrast nephropathy - it should not be used for diuresis as part of the preventative measures against radiocontrast-induced nephropathy.
- In elderly patients with dementia taking risperidone - Increased mortality (see below and section 4.5)

***Particular caution and/or dose reduction required*:**

- elderly patients (lower initial dose as particularly susceptible to side-effects - see section 4.2).
- difficulty with micturition including prostatic hypertrophy (increased risk of urinary retention: consider lower dose). Closely monitor patients with partial occlusion of the urinary tract
- in moderate liver congestion dosage adjustment may be needed
- diabetes mellitus (latent diabetes may become overt: insulin requirements in established diabetes may increase: stop furosemide before a glucose tolerance test)
- pregnancy (see section 4.6)
- gout (furosemide may raise uric acid levels/precipitate gout)
- impaired hepatic function – hepatic failure and alcoholic cirrhosis particularly predispose to hypokalaemia and hypomagnesaemia (see section 4.3 and below – monitoring required)
- impaired renal function and hepato-renal syndrome (see section 4.3 and below – monitoring required)
- adrenal disease (see section 4.3 – contraindication in Addison's disease)
- hypoproteinemia e.g. nephrotic syndrome (effect of furosemide may be impaired and its ototoxicity potentiated - cautious dose titration required).
- acute hypercalcaemia (dehydration results from vomiting and diuresis - correct before giving furosemide). Treatment of hypercalcaemia with a high dose of furosemide results in fluid and electrolyte depletion - meticulous fluid replacement and correction of electrolyte required
- premature infants – possible development of nephrocalcinosis/ nephrolithiasis (see below – monitoring of renal function required)
- some diuretics have been considered unsafe in acute porphyria
- symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with furosemide, particularly in the elderly, patients on other medications which can cause hypotension and patients with other medical conditions that are risks for hypotension.

Avoidance with other medicines (see also section 4.5 for other interactions)

- concurrent NSAIDs should be avoided – if not possible diuretic effect of furosemide may be attenuated
- ACE-inhibitors & Angiotensin II receptor antagonists – severe hypotension may occur – dose of furosemide should be reduced/stopped (3 days) before starting or increasing the dose of these

- concurrent risperidone in elderly patients with dementia has resulted in increased mortality – no mechanism for and no consistent pattern of deaths identified (see section 4.5)

***Laboratory and other monitoring requirements*:**

- Serum sodium

Particularly in the elderly or in patients liable to electrolyte deficiency

- Serum potassium

The possibility of hypokalaemia should be taken into account, in particular in patients with cirrhosis of the liver, those receiving concomitant treatment with corticosteroids, those with an unbalanced diet and those who abuse laxatives. Regular monitoring of the potassium, and if necessary treatment with a potassium supplement, is recommended in all cases, but is essential at higher doses and in patients with impaired renal function. It is especially important in the event of concomitant treatment with digoxin, as potassium deficiency can trigger or exacerbate the symptoms of digitalis intoxication (see section 4.5). A potassium-rich diet is recommended during long-term use.

Frequent checks of the serum potassium are necessary in patients with impaired renal function and creatinine clearance below 60ml/min per 1.73m2 body surface area as well as in cases where furosemide is taken in combination with certain other drugs which may lead to an increase in potassium levels (see section 4.5 & refer to section 4.8 for details of electrolyte and metabolic abnormalities)

- Renal function

Frequent BUN in first few months of treatment, periodically thereafter. Long-term/high-dose BUN should regularly be measured. Marked diuresis can cause reversible impairment of kidney function in patients with renal dysfunction. Adequate fluid intake is necessary in such patients. Serum creatinine and urea levels tend to rise during treatment. If used in premature infants there is a risk of nephrocalcinosis/nephrolithiasis so renal function must be monitored and renal ultrasonography performed

- Glucose

Adverse effect on carbohydrate metabolism - exacerbation of existing carbohydrate intolerance or diabetes mellitus. Regular monitoring of blood glucose levels is desirable.

- Other electrolytes

Patients with hepatic failure/alcoholic cirrhosis are particularly at risk of hypomagnesemia (as well as hypokalaemia). During long-term therapy (especially at high doses) magnesium, calcium, chloride, bicarbonate and uric acid should be regularly measured.

- Lipids

Serum cholesterol and triglycerides may rise but usually return to normal within 6 months of starting furosemide.

***Clinical monitoring requirements (see also section 4.8)*:**
Regular monitoring for

- blood dyscrasias. If these occur, stop furosemide immediately
- liver damage
- idiosyncratic reactions

Excipient Warnings

This product contains:

- Ethanol (Alcohol) – This medicine contains 79.5 mg of alcohol (ethanol) in each ml. The amount in 5ml of this medicine is equivalent to less than 10 ml beer or 4 ml wine. The amount of alcohol in this medicine is not likely to have an effect in adults and adolescents, and its effects in children are not likely to be noticeable. It may have some effects in younger children, for example feeling sleepy. The alcohol in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines. If you are pregnant or breast-feeding, talk to your doctor or pharmacist before taking this medicine. If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.

- Liquid maltitol (E 965) – Patients with rare hereditary problem of fructose intolerance should not take this medicine.

- Propylene Glycol (E1520) – This medicine contains 0.35 mg propylene glycol in each 5ml. If your baby is less than 4 weeks old, talk to your doctor or pharmacist before giving them this medicine, in particular if the baby is given other medicines that contain propylene glycol or alcohol.

- This medicine contains less than 1 mmol sodium (23 mg) per 5ml, that is to say essentially ‘sodium-free’.

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

Antihypertensives – enhanced hypotensive effect possible with all types. Concurrent use with ACE inhibitors or Angiotensin II receptor antagonists can result in marked falls in blood pressure, furosemide should be stopped or the dose reduced before starting an ACE-inhibitor or Angiotensin II receptor antagonists (see section 4.4). Increased risk of first dose hypotension with post-synaptic alpha-blockers (eg prazosin). Furosemide may interact with ACE inhibitors causing impaired renal function.

Aliskiren - reduces the plasma concentration of furosemide given orally. Reduced effect of furosemide might be observed in patients treated with both aliskiren and oral furosemide, and it is recommended to monitor for reduced diuretic effect and adjust the dose accordingly.

Antipsychotics – furosemide-induced hypokalaemia increases the risk of cardiac toxicity. Avoid concurrent use with pimozide. Increased risk of ventricular arrhythmias with pimozide (avoid concurrent use), amisulpride or sertindole. Enhanced hypotensive effect with phenothiazines.

In placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone. No consistent pattern for cause of death was observed but caution should be exercised and the risks and benefits of this combination considered prior to the decision to use.

Anti-arrhythmics (including amiodarone, disopyramide, flecainide and sotalol) - risk of cardiac toxicity (because of furosemide-induced hypokalaemia). The effects of lidocaine, tocainide or mexiletine may be antagonised by furosemide.

Cardiac glycosides – hypokalaemia and electrolyte disturbances (including hypomagnesemia) increase the risk of cardiac toxicity.

Drugs that prolong Q-T interval – increased risk of toxicity with furosemide induced electrolyte disturbances.

Vasodilators – enhanced hypotensive effect with moxisylyte (thymoxamine) or hydralazine.

Other diuretics – profound diuresis possible when furosemide given with metolazone. Increased risk of hypokalaemia with thiazides. Contraindicated with potassium sparing diuretics (e.g. amiloride spironolactone) - increased risk of hyperkalaemia (see section 4.3).

Renin inhibitors – aliskiren reduces plasma concentrations of furosemide.

Nitrates – enhanced hypotensive effect.

Lithium - furosemide reduces lithium excretion with increased plasma lithium concentrations (risk of cardio- and/or neuro-toxicity). Avoid concomitant administration unless plasma levels are monitored.

Chelating agents – sucralfate may decrease the gastro-intestinal absorption of furosemide – the 2 drugs should be taken at least 2 hours apart.

Lipid regulating drugs – Bile acid sequestrants (eg colestyramine: colestipol) – reduced absorption of furosemide – administer 2 to 3 hours apart.

NSAIDs – increased risk of nephrotoxicity (especially with pre-existing hypovolaemia/dehydration. Indometacin and ketorolac may antagonise the effects of furosemide (avoid if possible see section 4.4). In patients with dehydration or hypovolaemia, NSAIDs may cause acute renal insufficiency.

Salicylates – effects may be potentiated by furosemide. Salicylic toxicity may be increased by furosemide.

Antibiotics – increased risk of ototoxicity with aminoglycosides, polymixins or vancomycin - only use concurrently if compelling reasons. Increased risk of nephrotoxicity with aminoglycosides or cefaloridine. Furosemide can decrease vancomycin serum levels after cardiac surgery. Increased risk of hyponatraemia with trimethoprim. Concurrent use with tetracyclines may increase the risk of rising BUN (see section 4.4 – monitoring).

Antiviral – plasma concentrations of diuretics may be increased by nelfinavir, ritonavir or saquinavir.

Antidepressants – enhanced hypotensive effect with MAOIs. Increased risk of postural hypotension with TCAs (tricyclic antidepressants). Increased risk of hypokalaemia with reboxetine.

Antidiabetics – hypoglycaemic effects antagonised by furosemide.
Insulin - requirements may be increased (see section 4.4).

Antiepileptics – increased risk of hyponatraemia with carbamazepine. Diuretic effect reduced by phenytoin.

Antihistamines – hypokalaemia with increased risk of cardiac toxicity.

Antifungals – increased risk of hypokalaemia and nephrotoxicity with amphotericin.

Anxiolytics and hypnotics – enhanced hypotensive effect. Chloral hydrate or triclofos may displace thyroid hormone from binding site.

CNS stimulants (drugs used for ADHD) – hypokalaemia increases the risk of ventricular arrhythmias.

Corticosteroids – diuretic effect antagonised (sodium retention) and increased risk of hypokalaemia.

Cytotoxics – increased risk of nephrotoxicity and ototoxicity with platinum compounds/cisplatin.

Anti-metabolites – effects of furosemide may be reduced by methotrexate and furosemide may reduce renal clearance of methotrexate.

Potassium salts – contraindicated - increased risk of hyperkalaemia (see section 4.3).

Dopaminergics – enhanced hypotensive effect with levodopa.

Immunomodulators – enhanced hypotensive effect with aldesleukin. Increased risk of hyperkalaemia with ciclosprin and tacrolimus. Increased risk of gouty arthritis with ciclosporin.

Muscle relaxants – enhanced hypotensive effect with baclofen or tizanidine. Increased effect of curare-like muscle relaxants.

Oestrogens – diuretic effect antagonised.

Progestogens (drospirenone) – increased risk of hyperkalaemia and diuretic effect antagonised.

Prostaglandins – enhanced hypotensive effect with alprostadil.

Sympathomimetics – increased risk of hypokalaemia with high doses of $beta_2$ sympathomimetics.

Theophylline – enhanced hypotensive effect.

Probenecid –effects of furosemide may be reduced by probenecid and furosemide may reduce renal clearance of probenecid.

Anaesthetic agents – general anaesthetic agents may enhance the hypotensive effects of furosemide. The effects of curare may be enhanced by furosemide.

Warfarin and clofibrate – compete with furosemide in binding to serum albumin – possibly significant if this is low (eg nephrotic syndrome).

Aminoglutethimide – concomitant use may increase the risk of hyponatraemia.

Alcohol – enhanced hypotensive effect.

Laxative abuse - increases the risk of potassium loss.

Liquorice - excess intake may increase the risk of hypokalaemia.

4.6. Fertility, pregnancy and lactation

Pregnancy

Frusol must not be given during pregnancy unless there are compelling medical reasons.

Breast-feeding

Furosemide may inhibit lactation and may pass into breast milk. Women must not breastfeed if they are treated 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

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); Frequency not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:	Uncommon:	aplastic anaemia
	Rare:	bone marrow depression (necessitates withdrawal of treatment), eosinophilia, leucopenia.
	Very rare:	haemolytic anaemia, agranulocytosis, thrombocytopenia
Metabolism and nutritional disorders:	Very common:	dehydration, hyponatraemia, hypochloremic metabolic alkalosis, hypocalcaemia, hypomagnesemia (incidences of the last three are reduced by triamterene)
	Common:	Hypovolaemia, hypochloraemia
	Uncommon:	impaired glucose tolerance (by hypokalaemia) hyperuricaemia, gout, reduction of serum HDL-cholesterol, elevation of serum LDL-cholesterol, elevation of serum triglycerides, hyperglycaemia.
	Very rare:	tetany
	Frequency not known:	aggravated pre-existing metabolic alkalosis (in decompensated cirrhosis of the liver), fluid and electrolyte disturbances, excretion of potassium increased* In patients with diabetes mellitus this may lead to deterioration of metabolic control; latent diabetes mellitus may become manifest
Psychiatric disorder:	Rare:	psychiatric disorder NOC
Nervous system disorders:	Rare:	paraesthesia, confusion, headache
	Not known:	dizziness, fainting and loss of consciousness (caused by symptomatic hypotension)
Eye disorders:	Uncommon:	visual disturbance, blurred vision, yellow vision.

Ear and labyrinth disorders:	Uncommon:	deafness (sometimes irreversible)
	Rare:	tinnitus and reversible or irreversible loss of hearing (although usually transitory, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephritic syndrome)
Cardiac disorders:	Uncommon:	orthostatic intolerance, cardiac arrhythmias, increased risk or persistence of patent ductus arteriosus in premature infants.
Vascular disorders:	Very common:	hypotension, (which, if pronounced may cause signs and symptoms such as impairment of concentration and reactions, light-headedness, sensations of pressure in the head, headache, drowsiness, weakness, disorders of vision, dry mouth, orthostatic intolerance).
	Rare:	vasculitis, thrombosis, shock
Gastrointestinal disorders:	Uncommon:	dry mouth, thirst, nausea, bowel motility disturbances, vomiting, diarrhoea, constipation
	Rare:	acute pancreatitis (in long-term diuretic treatment, including furosemide).
Hepatobiliary disorders:	Rare:	pure intrahepatic cholestasis (jaundice), hepatic function abnormal.
	Frequency not known:	Hepatic encephalopathy in patients with hepatocellular insufficiency may occur.
Skin and subcutaneous tissue disorders:	Rare:	rash, pruritus, photosensitivity, toxic epidermal necrolysis.
	Frequency not known:	urticaria, erythema multiforme, purpura, exfoliative dermatitis, itching, allergic reactions, such as skin rashes, various forms of dermatitis including urticaria, bullous lesions, acute generalised exanthematous pustulosis (AGEP). When these occur treatment should be withdrawn. Steven-Johnson's syndrome
Musculoskeletal and connective tissue disorders:	Uncommon:	muscle cramps, muscle weakness.
Renal and urinary disorders:	Very common:	nephrocalcinosis in infants
	Uncommon:	reduced diuresis, urinary incontinence, urinary obstruction (in

		patients with hyperplasia of the prostate, bladder inability to empty, urethral stricture unspecified).
	Rare:	interstitial nephritis, acute renal failure.
Congenital, familial and genetic disorders:	Rare:	patent ductus arteriosus
General disorders and administration site conditions:	Uncommon:	Fatigue
	Rare:	malaise, fever, severe anaphylactoid or anaphylactic reactions (e.g. with shock).
Investigations:	Common:	creatinine increased, blood urea increased
	Rare:	Transaminases increased, blood

*Potassium deficiency manifests itself in neuromuscular symptoms (muscular weakness, paralysis), intestinal symptoms (vomiting, constipation meterorism), renal symptoms (polyuria) or cardiac symptoms. Severe potassium depletion can result in paralytic ileus or confusion, which can result in coma.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

4.9. Overdose

Symptoms
Overdosing may lead to dehydration and electrolyte depletion through excessive diuresis. Severe potassium loss may lead to serious cardiac arrhythmias.

Management
Treatment of overdose consists of fluid replacement and electrolyte imbalance correction.

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: High-Ceiling Diuretic Sulfonamide –
ATC code: 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

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 ß 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

Furosemide is a widely used diuretic which has been available for over thirty years and its safety profile in man is well established.

6.1. List of excipients

Ethanol, sodium hydroxide, cherry flavour (containing ethanol and propylene glycol (E1520)), liquid maltitol (E965), disodium hydrogen phosphate (E339), citric acid monohydrate (E330) and purified water.

6.2. Incompatibilities

None known

6.3. Shelf life

24 months
3 months after first opening

6.4. Special precautions for storage

Store at or below 25°C.

6.5. Nature and contents of container

Bottles: Amber (Type III) glass

Closures: HDPE, EPE wadded, tamper evident, child resistant

Capacity: 150ml

6.6. Special precautions for disposal and other handling

Keep out of the sight and reach of children.

Instruction for administration via nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes:

Ensure that the enteral feeding tube is free from obstruction before administration.

1. Flush the enteral tube with water, a minimum flush volume of 5mL is required.
2. Administer the required dose of Furosemide Oral Solution gently and slowly into enteral tube, with a suitable measuring device.
3. Flush the enteral tube with water again. A minimum flush volume of 5mL is required. However, for large bore size tubes (18 Fr) a minimum flush volume of 10mL should be used.

This product has not been tested with latex NG or PEG tubes and therefore should not be used with tubes made from latex.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

PL 00427/0111

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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