SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

FUROSEMIDE TABLETS BP 40mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 40mg Furosemide PhEur.

Excipients with known effect:
Each tablet contains 75mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White uncoated tablets.

White, circular, flat bevelled-edge uncoated tablets, impressed with the identifying letters “F” and “D” on either side of a central division line on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Furosemide is a diuretic recommended for use in all indications where a prompt and effective diuresis is required.
Indications for furosemide include:
1) The treatment of oedema associated with congestive heart failure, cirrhosis of the liver, renal disease including nephrotic syndrome and pulmonary oedema.
2) The treatment of peripheral oedema due to mechanical obstruction, venous insufficiency, mild to moderate hypertension.

4.2 Posology and method of administration

Posology
Adults and children over 12 years:
Oedema: Initially 40mg daily in the morning; ordinarily a prompt diuresis ensues and the starting dose can then be maintained or even reduced. Diuresis lasts for approximately four hours following administration and hence the time of administration can be adjusted to suit the patient's requirements. Maintenance dose is 20mg daily or 40mg on alternate days, increased in resistant oedema to 80mg daily.
Hypertension: 20-40mg twice daily; if 40mg twice daily does not lead to a clinically satisfactory response, the addition of other antihypertensive agents, rather than an increase in the dose of furosemide should be considered.
Children under 12 years: A more suitable dosage form should be used in this age group.
Elderly: Furosemide is generally eliminated more slowly. The dosage should be titrated until the required response is achieved.

Method of Administration
For oral administration.

Dosage adjustment may be required (see also section 4.4)
Dosage adjustment may be necessary in patients with

- hypoproteinaemia
- liver congestion/dysfunction.

Concomitant administration of the following with furosemide should be considered (see section 4.4):
Colestyramine and colestipol - Administer 2 to 3 hours apart.

4.3 Contraindications

Furosemide is contraindicated in the following circumstances

- Hypersensitivity to furosemide, any of its excipients, sulfonamides, sulfonamide derivatives/amiloride or to any of the excipients listed in section 6.1
- Anuria and impaired renal function (creatinine clearance below 30mL/min per 1.73 m2 body surface area) and renal failure resulting from poisoning by nephrotoxic and/or hepatotoxic agents
- Electrolyte disturbances (severe hyponatraemia: severe hypokalaemia, hypovolaemia), dehydration and/or hypotension (see section 4.4)

- Concomitant potassium supplements or potassium sparing diuretics (see section 4.5)
- Pre-coma/coma associated with hepatic cirrhosis or encephalopathy
- Addison's disease (see section 4.4)
- Digitalis intoxication (see also section 4.5)
- Breast-feeding women (see 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.

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.

Particular caution and/or dose reduction required:
- elderly patients
- difficulty with micturition/ potential obstruction in the urinary tract including prostatic hypertrophy (increased risk of acute retention)
- diabetes mellitus (latent diabetes may become overt: insulin requirements in established diabetes may increase: stop furosemide before a glucose tolerance test)
- gout (furosemide may raise uric acid levels/precipitate gout)
- patients with hepatorenal syndrome
- impaired hepatic function (see section 4.3 and below – monitoring required)
- impaired renal function (see section 4.3 and below – monitoring required)
- hypoproteinaemia e.g. nephrotic syndrome (effect of furosemide may be impaired and its risk of ototoxicity potentiated - cautious dose titration required)
- in moderate liver congestion dosage adjustment may be needed
- patients who are at risk from a pronounced fall in blood pressure.

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.

Laboratory 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 1.73m^2 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.

- 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 hypomagnesia (as well as hypokalaemia). During long-term therapy (especially at high doses) magnesium, calcium, chloride, bicarbonate and uric acid should be regularly measured.

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

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

In premature infants there is a risk of development of nephrocalcinosis/nephrolithiasis. Renal function must be monitored and renal ultrasonography performed.

Other alterations in lab values

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

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption 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.

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.

Angiotensin-II Receptor Antagonists - enhanced hypotensive effect when diuretics given with angiotensin-II receptor antagonists.

Antipsychotics - hypokalaemia caused by diuretics increase the risk of ventricular arrhythmias with amisulpride 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).

Risperidone - when administering risperidone, caution should be exercised and the risks and benefits of the combination or co-treatment with furosemide or with other potent diuretics should be considered prior to the decision to use. Increased mortality has been observed in elderly patients with dementia concomitantly receiving risperidone.

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

Cardiac glycosides – hypokalaemia caused by loop diuretics increases cardiac toxicity with cardiac glycosides.

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.

Renin inhibitors – 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.

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 hyperkalaemia 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.

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

Analgesics – diuretics can increase the risk of nephrotoxicity of NSAIDs, also antagonism of diuretic effect. Antagonism of diuretic effect (especially with Indometacin and Ketorolac). Salycylic toxicity may be increased by furosemide.

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.

Ciclosporin - there is an increased risk of nephrotoxicity and possibly hypermagnesaemia when diuretics are given with ciclosporin.

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 antagonized by phenytoin.

Antifungals – there is an increased risk of hypokalaemia when loop diuretics are given with amphoterecin.

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.

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

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.

Dopaminergics – enhanced hypotensive effect with levodopa.

Muscle relaxants – enhanced hypotensive effect with baclofen or tizanidine.

Oestrogens and progestogens – diuretic effect antagonized.

Prostaglandins – enhanced hypotensive effect with alprostadil.

Sympathomimetics, Beta$_2$ – there is an increased risk of hypokalaemia when loop diuretics are given with high doses of beta$_2$ 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.

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.

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

Alcohol – enhanced hypotensive effect.

Carbenoxolone, prolonged use of laxatives, liquorice - may increase the risk of developing hypokalaemia.

4.6 Fertility, pregnancy and lactation

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. Treatment during pregnancy requires monitoring of foetal growth.

Breast-feeding
Furosemide passes into breast milk and may inhibit lactation. Women must not breastfeed if they are treated with furosemide.

Fertility
No human data on the effect of furosemide on fertility are available.

4.7 Effects on ability to drive and use machines

Reduced mental alertness and rarely dizziness and blurred vision have been reported. Patients so affected should not drive or operate machinery.

4.8 Undesirable effects

The following classification of CIOMS frequencies according to the MedDRA database is used where applicable: 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); 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), nephrocalcinosis in infants
	Common	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
Psychiatric disorder	Rare	psychiatric disorder
Nervous system disorders	Rare	paraesthesia, confusion, headache, dizziness
	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)
	Common	hypovolaemia
	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
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.
Musculoskeletal and connective tissue disorders	Uncommon	muscle cramps, muscle weakness
Renal and urinary disorders	Uncommon	reduced diuresis, urinary incontinence, urinary obstruction (in patients with hyperplasia of the prostate, bladder inability to empty, urethral stricture unspecified)
	Rare	nephrocalcinosis (in pre-term infants treated with furosemide), 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

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; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

a) Signs and symptoms

The clinical picture in acute or chronic over dosage depends primarily on the extent and consequences of loss of electrolytes and fluids (e.g. hypovolemia, dehydration, hemoconcentration, cardiac arrhythmia - including A-V block and ventricular fibrillation). Symptoms of these changes include: severe hypotension (and progression to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

b) Treatment

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. use of activated charcoal).

Changes in clinically relevant fluid and electrolyte balance must be corrected. Together with the prevention and treatment of serious complications resulting from such imbalances and other effects on the body, this corrective action may require intensive generalist and specific medical monitoring, as well as of therapeutic measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 3.4.1.2 - Cardiovascular apparatus. Antihypertensives. Diuretics, Diuretics of loop, ATC code: C03CA01

Mechanism of action:

Furosemide is a potent, fast-acting diuretic with a rapid onset of action. From the pharmacological point of view, furosemide inhibits co-transport system (reabsorption) of the Na +, K + and $2Cl^-$ electrolytes, located of the luminal cell membrane of the ascending limb of the loop of Henle consequently, the efficacy of the saluretic action of furosemide depends on the product reaches the tubular lumen through a transport mechanism anionic. Diuretic action results from the inhibition of sodium chloride reabsorption in this segment of the loop of Henle. As a result, fractional sodium excretion can amount to as much as 35% of sodium filtered by the glomeruli filtration. As a result of increased sodium excretion, there is increased urine excretion and a rise in potassium secretion in the distal tubules. The excretion of calcium and magnesium ions is increased.

Furosemide disrupts the tubulo-glomerular feedback mechanism in the macula dense, resulting in non- attenuation of saluretic activity. Furosemide causes dose-dependent stimulation of the renin-angiotensin- aldosterone system.

In case of heart failure, furosemide causes an acute reduction in preload (by increasing the capacitance of blood vessels). This vascular effect seems to be mediated by prostaglandins and with the activation of the renin-angiotensin

system and an intact synthesis of prostaglandins. Furosemide decreases the vascular reactivity to catecholamines, which is increased in hypertensive patients.

The antihypertensive efficacy of furosemide is attributable to increased excretion of sodium, blood volume reduction and vascular smooth muscle response to the stimulus vasoconstrictor.

5.2 Pharmacokinetic properties

Furosemide is rapidly absorbed from the gastrointestinal tract. The tmax is 1 to 1.5 hours in the case of Furosemide 40 mg. Absorption of the drug denotes a broad intra and interindividual variability.

The bioavailability of furosemide in healthy volunteers is approximately 50% - 70% for tablets. In the case of sick individuals, the bioavailability of drug is influenced by several factors, including concomitant diseases, and can be reduced by around 30% (for example in the case of nephrotic).

The absorption of furosemide may be affected by food intake and effect seems to depend on the pharmaceutical formulation in question. The volume of distribution of furosemide is 0.1 to 1.2 liters per kg of body weight.

The plasma protein binding (mostly to albumin) is greater than 98%. Furosemide is mostly eliminated in the non-conjugated form, mainly by secretion at the level of the proximal tubule. Following intravenous administration, 60% to 70% of the furosemide dose is excreted in this way. The glucuronic metabolite of furosemide represents 10% to 20% of the substances recovered in the urine.

The remaining dose is excreted in the faeces, probably after biliary secretion.

The terminal half-life of furosemide after intravenous administration is approximately 1 to 1.5 hours. Furosemide is excreted in breast milk. Furosemide crosses the barrier the placenta slowly transferring to the fetus. Furosemide reaches concentrations identical in the mother and in the fetus or newborn.

Renal insufficiency
In case of renal insufficiency, the elimination of furosemide is slower and its half-life is prolonged, the terminal half-life may reach 24 hours in patients with severe renal impairment.

In case of nephrotic syndrome, the lower concentration of plasma proteins leads to higher concentrations of unconjugated (free) furosemide. On the other hand, the efficacy of furosemide is reduced in these patients, due to the intratubular albumin and decreased tubular secretion.

Furosemide is poorly dialysable in patients receiving hemodialysis, dialysis peritoneal or CAPD (Chronic Ambulatory Peritoneal Dialysis).

Hepatic/Renal insufficiency
In case of hepatic impairment, the half-life of furosemide is in the order of 30% to 90%. In addition, elimination of furosemide is slowed due to reduced renal function in patients with congestive heart failure, severe hypertension, or in the elderly.

Premature and newborn infants
Depending on the maturity of the kidney, elimination of furosemide may be slower. The metabolism of the drug is also reduced in the case of children with insufficiency of glucuronization capacity. The terminal half-life is less than 12 hours in children with a post-conception age greater than 33 weeks. In children with terminal age is equal to that of adults.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Also contains: lactose, magnesium stearate, maize starch, stearic acid.

6.2 Incompatibilities

None known.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store below 25°C in a dry place.

Protect from light.

6.5 Nature and contents of container

The product is supplied in blister packs and cartons:
a) Carton: Printed carton manufactured from white folding box board.
b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil.

Pack sizes: 28s, 30s, 50s, 56s, 60s, 84s, 90s, 100s, 112s, 120s, 168s, 180s, 250s, 500s, 1000s

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
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EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 0142/0371

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/02/1994 / 11/03/1999

10 DATE OF REVISION OF THE TEXT

15/05/2026