SCHEDULING STATUS

S3

1.NAME OF THE MEDICINE

Furosemide 40 Biotech (Capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 40 mg furosemide.

Excipient with known effect:

Each capsule contains 90,0 mg lactose.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

Opaque white body/opaque turquoise blue cap, size '2' snap-fit capsule containing white, lump-free powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of oedema of cardiac, hepatic or renal origin. In the management of refractory oedema, it may be used in conjunction with other types of diuretics, particularly the potassium-sparing medicines.

4.2 Posology and method of administration

In most cases 40 mg daily will suffice. If no response is obtained, this dose may be increased after 6

hours to 80 mg and - if necessary - after another 6 hours to 120 mg. Daily doses of more than 120 mg should preferably be distributed over 2 - 3 individual doses. After mobilising the oedema, maintenance therapy is continued i.e., 20 to 40 mg daily. Children generally receive daily oral doses of 1 mg/kg body weight. If necessary, this dose may be increased step by step to a maximum of 3 mg/kg body weight per day. A dose of 120 mg per day should not be exceeded with children.

Method of administration

For oral administration.

4.3 Contraindications

Patients who exhibit hypersensitivity to furosemide, sulphonamides, or to any of the excipients as listed in section 6.1.

Furosemide 40 Biotech is contraindicated if increasing azotaemia and oliguria occurs during treatment of severe progressive renal disease, anuria, hypokalaemia, hyponatraemia, hypovolaemia with or without hypotension, dehydration - in these cases the medicine should be discontinued. Drug induced renal failure and renal failure associated with hepatic coma. In hepatic coma and in states of electrolyte depletion, therapy with Furosemide 40 Biotech should not be instituted until the basic condition is corrected or improved.

Furosemide 40 Biotech should not be given to lactating women (see section 4.6).

4.4 Special warnings and precautions for use

Hypotension and/or hypovolaemia (see also section 4.3)

These and any acid-base disturbances should be corrected before Furosemide 40 Biotech is started.

Symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with Furosemide 40 Biotech, particularly in the elderly, patients on other medications which can cause hypotension and patients with other medical conditions that are risks for hypotension.

Dose titration/adjustment

- Patients with hypoproteinaemia (such as that associated with the nephrotic syndrome) require careful dose titration (reduced furosemide effect: increased risk of ototoxicity).
- In moderate liver congestion dosage adjustment may be needed

Caution required:

Caution needed in the following circumstances

- impaired hepatic function
- impaired renal function and hepato-renal syndrome (see section 4.3 and below – monitoring required)
- diabetes mellitus (latent diabetes may become overt: insulin requirements in established diabetes may increase)
- elderly patients
- difficulty with micturition/potential obstruction in the urinary tract including prostatic hypertrophy (increased risk of acute retention)
- gout (increased risk of hyperuricaemia)
- patients at risk of pronounced falls in blood pressure

Clinical monitoring requirements (see also section 4.8):

Regular monitoring for

- blood dyscrasias. If these occur, stop Furosemide 40 Biotech 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.

Laboratory monitoring requirements:

- frequent BUN in first few months of treatment, periodically thereafter
- serum electrolytes with replacement as appropriate

Other alterations in lab values

- Serum creatinine and urea levels tend to rise during treatment
- Serum cholesterol and triglycerides may rise but usually return to normal within 6 months of starting Furosemide 40 Biotech
- Furosemide 40 Biotech should be discontinued before a glucose tolerance test

Not to be used in the first trimester of pregnancy.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Antihypertensives - enhanced hypotensive effect possible with all types. Concurrent use with ACE inhibitors can result in marked falls in blood pressure. Furosemide 40 Biotech should be stopped or the dose reduced before starting an ACE-inhibitor. There is a risk of a first-dose effect with post-synaptic alpha blockers e.g., prazosin. Furosemide 40 Biotech may interact with ACE inhibitors causing impaired renal function.

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

Anti-dysrhythmics (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 40 Biotech.

Medicines associated with QT prolongation – cardiac toxicity may be increased by furosemide-induced hypokalaemia and/or hypomagnesaemia.

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

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

Renin inhibitors – aliskiren reduces plasma concentrations of Furosemide 40 Biotech.

Nitrates – enhanced hypotensive effect.

Lithium – Furosemide 40 Biotech reduces lithium excretion with increased plasma lithium concentrations (risk of toxicity). Avoid concomitant administration unless plasma levels are monitored.

Chelating medicines – sucralfate may decrease the gastro-intestinal absorption of Furosemide 40 Biotech – the 2 medicines should be taken at least 2 hours apart.

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

NSAIDs – increased risk of nephrotoxicity (especially if there is hypovolaemia). Indomethacin and ketorolac may antagonise the effects of Furosemide 40 Biotech. In patients with dehydration or hypovolaemia, NSAIDs may cause acute renal insufficiency.

Salicylates – effects may be potentiated by Furosemide 40 Biotech.

Antibiotics– increased risk of ototoxicity with aminoglycosides, polymixins or vancomycin. Increased risk of nephrotoxicity with aminoglycosides or cefaloridine. Furosemide 40 Biotech can decrease vancomycin serum levels after cardiac surgery.

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

Antidiabetics – hypoglycaemic effects antagonised by Furosemide 40 Biotech.

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 with amphotericin.

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

CNS stimulants (medicines used for ADHD) – hypokalaemia increases the risk of ventricular dysrhythmias.

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

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

Other diuretics – profound diuresis possible when furosemide given with metolazone. Increased risk of hypokalaemia with thiazides.

Dopaminergics – enhanced hypotensive effect with levodopa.

Immunomodulators – enhanced hypotensive effect with aldesleukin.

Muscle relaxants – enhanced hypotensive effect with baclofen or tizanidine (see also Anaesthetic medicines below – curare).

Oestrogens and progestogens – diuretic effect antagonized.

Prostaglandins – enhanced hypotensive effect with alprostadil.

Sympathomimetics – increased risk of hypokalaemia with high doses of $beta_2$ sympathomimetics (such as bambuterol, formoterol, salbutamol, salmeterol and terbutaline).

Theophylline – enhanced hypotensive effect.

Probenecid – reduced renal clearance of furosemide and decreased diuretic effect.

Anaesthetic medicines – general anaesthetic medicines may enhance the hypotensive effects of furosemide. The effects of curare may be enhanced by Furosemide 40 Biotech.

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

There is little evidence of safety of high-dose furosemide in human pregnancy, although the results of animal work, in general, show no hazardous effects.

Breastfeeding

Furosemide 40 Biotech may inhibit lactation or may pass into the breast milk, it should therefore not be used during lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

Patients should be warned that reduced mental alertness may impair ability to drive or operate dangerous machinery.

4.8 Undesirable effects

MedDRA System Organ Class		**Description**
Blood and lymphatic system disorders	Less frequent	aplastic anaemia, bone marrow depression (necessitates withdrawal of treatment), eosinophilia, leukopenia, haemolytic anaemia, agranulocytosis, thrombocytopenia
Metabolism and nutrition disorders	Frequent	dehydration, hyponatraemia, hypochloraemia metabolic alkalosis, hypocalcaemia, hypomagnesemia (incidences of the last three are reduced by triamterene), hypovolaemia, hypochloraemia
	Less Frequent	impaired glucose tolerance (by hypokalaemia) hyperuricaemia, gout, reduction of serum HDL-cholesterol, elevation of serum LDL-cholesterol, elevation of serum triglycerides, hyperglycaemia, tetany
	Frequency unknown	aggravated pre-existing metabolic alkalosis (in decompensated cirrhosis of the liver), fluid and

		electrolyte disturbances, excretion of potassium increased*
Psychiatric disorder	Less frequent	psychiatric disorder NOC
Nervous system disorders	Less frequent	paraesthesia, confusion, headache
	Frequency unknown	dizziness, fainting and loss of consciousness (caused by symptomatic hypotension)
Eye disorders	Less frequent	visual disturbance, blurred vision, yellow vision
Ear and labyrinth disorders	Less frequent	deafness (sometimes irreversible), 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	Less frequent	orthostatic intolerance, cardiac dysrhythmias, increased risk or persistence of patent ductus arteriosus in premature infants
Vascular disorders	Frequent	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)
	Less frequent	vasculitis, thrombosis, shock
Gastro-intestinal disorders	Less frequent	dry mouth, thirst, nausea, bowel motility disturbances, vomiting, diarrhoea, constipation, acute pancreatitis (in long-term diuretic treatment, including furosemide)
Hepato-biliary disorders	Less frequent	pure intrahepatic cholestasis (jaundice), hepatic function abnormal

Skin and sub-cutaneous tissue disorders	Less frequent	rash, pruritus, photosensitivity, toxic epidermal necrolysis
	Frequency unknown	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, Stevens-Johnson syndrome
Musculo-skeletal and connective tissue disorders	Less frequent	muscle cramps, muscle weakness
Renal and urinary disorders	Frequent	nephrocalcinosis in infants
	Less frequent	reduced diuresis, urinary incontinence, urinary obstruction (in patients with hyperplasia of the prostate, bladder inability to empty, urethral stricture unspecified), acute renal failure, interstitial nephritis
Congenital, familial and genetic disorders	Less frequent	patent ductus arteriosus
Congenital, familial and genetic disorders	Less frequent	patent ductus arteriosus
Investigations	Frequent	creatinine increased; blood urea increased
	Less frequent	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 medicine is important. It allows continued monitoring of the benefit/ risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Fluid and electrolyte depletion is the most serious danger of overdosage. Treatment should therefore be aimed at electrolyte and fluid replacement.

The medicine should be discontinued, and electrolyte and water replacement instituted immediately; adjustment should be on the basis of careful monitoring.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 18.1 Diuretics

ATC code: CO3C A01

Furosemide is a diuretic and is readily absorbed from the gastrointestinal tract. Considerable portions are bound to plasma proteins. It is rapidly excreted in the urine by both glomerular filtration and tubular secretion, the latter accounts for roughly two thirds of the ingested dose. The remainder is excreted in the faeces.

Furosemide exerts its diuretic action by virtue of its saluretic properties. It acts primarily to inhibit sodium and chloride reabsorption in the ascending limb of the loop of Henle.

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 4 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 bound to plasma albumin and little biotransformation takes place. 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.

In renal/ hepatic impairment

Where liver disease is present, biliary elimination is reduced up to 50 %. Renal impairment has little effect on the elimination rate of furosemide, but less than 20 % residual renal function increases the elimination time.

The elderly

The elimination of furosemide is delayed in the elderly where a certain degree of renal impairment is present.

Newborn

A sustained diuretic effect is seen in the newborn, possibly due to immature tubular function.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal Silicon Dioxide (Aerosil 200)

Purified talc

Lactose

Empty cap and empty body

Elanco Opaque Blue 50

Brilliant Blue CI 42090

Erythrosine CI 45430

Elanco Opaque White

Gelatin

Titanium Dioxide CI 77891

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C in a cool place. Protect from light.

6.5 Nature and contents of container

Furosemide 40 Biotech capsules are available in transparent PVC/PVDC/Aluminium blister packs of 30 capsules. Each blister strip contains 10 capsules, and 3 blister strips are packed in an outer carton.

White, opaque, round HDPE bottles with white, opaque PP CT cap with wad having induction sealing liner.

Pack size: 30, 100, 112, 250, 1 000

White HDPE securitainer with white LDPE tear-off cap and foam disc (wadding).

Pack size: 30, 100

Patient ready packs (PRP's) are available in pack sizes of 28, 56 or 84 capsules.

All pack sizes may not necessarily be marketed at one time.

6.6 Special precautions for disposal and other handling

No special precautions

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor, Block K West, Central Park

400 16th Road, Randjespark, Midrand, 1685

South Africa

8. REGISTRATION NUMBER

R/18.1/5

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

November 1989

10. DATE OF REVISION OF THE TEXT

16 November 2023