SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

BURINEX 1 mg (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains bumetanide 1 mg.
Contains sugar: Lactose 51,4 mg per tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

White, flat (8 mm), circular, uncoated, bevelled edge tablet, marked on one face with a score line and with the number “133” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BURINEX is indicated for the treatment of oedema, e.g. that associated with congestive heart failure, renal disease, acute pulmonary oedema, hepatic ascites.

4.2 Posology and method of administration

Posology

The following recommendations are based on clinical experience to date:
Most patients require a daily dose of 1 mg which can be given as a single morning dose. Depending on the patient's response a second dose can be given six to eight hours later. In refractory cases, the dose can be increased until a satisfactory diuretic response is obtained.

The dose should be carefully titrated in each patient according to the patient's response and the required therapeutic activity. As a general rule, in patients not controlled on lower doses, dosage should be started at 5 mg daily and then increased by 5 mg increments every twelve to twenty-four hours until the required response is obtained or side effects appear.

Consideration should be given to twice daily dosage rather than once daily.

Paediatric population

Until further experience of paediatric use is accumulated, BURINEX should not be given to children.

Method of administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance, bumetanide or to any of the excipients listed in section 6.1.
- Anuria. Although BURINEX can be used to induce diuresis in renal insufficiency, any marked increase in blood urea or the development of oliguria during treatment of severe progressive renal disease is an indication for stopping treatment with BURINEX.
- BURINEX is contraindicated in hepatic coma and in acute cases of moderately severe or severe liver failure. This does not preclude its use in treatment of ascites due to hepatic cirrhosis, but such therapy is best initiated in hospital.
- BURINEX is contraindicated in states of electrolyte depletion.

4.4 Special warnings and precautions for use

Excessively rapid mobilisation of oedema, particularly in elderly patients, may give rise to sudden changes in cardiovascular pressure relationships with circulatory collapse and should be borne in mind when BURINEX is given in high doses orally.

Electrolyte imbalance

Electrolyte disturbance is likely to occur in those patients treated with high doses or for prolonged periods, particularly in those patients taking a low salt diet. Periodic checks of serum electrolyte levels, in particular sodium, potassium, chlorides and bicarbonates should be undertaken and where necessary replacement therapy instituted.

The precautions to be taken with BURINEX are mainly those associated with electrolyte disturbance. Electrolyte depletion may show itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting or mental confusion. Patients in whom a risk of depletion is likely, should undergo periodic serum electrolyte determinations (see section 4.8).

BURINEX increases the excretion of potassium. This may cause the gradual development of low serum potassium levels. Patients on long-term treatment should, therefore, be encouraged to take a high potassium diet. Potassium chloride supplements are indicated in those patients whose dietary potassium is possibly inadequate, the chloride tending to correct the hypochloraemia and metabolic alkalosis, which is occasionally associated with potassium depletion. Potassium sparing diuretics, such as spironolactone, have been used as an alternative approach. Studies have shown that continued daily administration of BURINEX for several months, supplemented with either potassium chloride or spironolactone produced an effective diuresis with minimal changes in serum electrolytes. Low serum potassium levels, it should be noted, increase the sensitivity of the myocardium to the toxic effects of digitalis.

It is also important to prevent hypokalaemia in patients with hepatic cirrhosis. Potassium supplements are also indicated in conditions associated with a particular tendency to potassium depletion, e.g., long-term treatment with corticosteroids, ulcerative colitis, prolonged vomiting or diarrhoea.

Hepatic Impairment
Encephalopathy may be precipitated in patients with pre-existing hepatic impairment.

Hypotension
Caution should be exercised when BURINEX is used in patients with hypotension.

Hyperuricaemia
BURINEX may cause an increase in blood uric acid.

Renal Impairment
Patients with chronic renal failure on high doses of BURINEX should remain under constant hospital supervision.

Diabetic patients
Periodic checks on urine and blood glucose should be made in diabetics and patients suspected of latent diabetes.

Hypersensitivity
Patients allergic to sulfonamides may show hypersensitivity to BURINEX.

Excipient warning
BURINEX tablets contain lactose as an excipient and patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take BURINEX.

4.5 Interaction with other medicines and other forms of interaction
Dose adjustment of hypoglycaemic medicines may be necessary in patients with diabetes mellitus.

Digitalis glycosides
Hypokalaemia increases the sensitivity to digitalis glycosides which might result in digitalis toxicity (nausea, vomiting, and dysrhythmias). Potassium level and signs for digitalis toxicity should be monitored. Therefore, the dose of bumetanide may need adjustment when given in conjunction with cardiac glycosides.

Non-depolarising neuromuscular blocking medicines
Hypokalemia increases the sensitivity to non-depolarising neuromuscular blocking medicines.

Antihypertensive medicines and medicines inducing postural hypotension
BURINEX may potentiate the effect of antihypertensive medicines. Therefore, patients taking these medicines should be monitored and dosage adjustment should occur where necessary.

NSAIDs
Certain non-steroidal anti-inflammatory drugs have been shown to antagonise the action of

diuretics.

Lithium
BURINEX reduces lithium clearance resulting in high serum levels of lithium. This may result in increased lithium toxicity, including increased risk of cardiotoxic and neurotoxic effects of lithium. Therefore, it is recommended that lithium levels are carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination.

Anti-dysrhythmics
Concomitant use of BURINEX and class III anti-dysrhythmic medicines may result in increased risk of electrolyte imbalance and subsequent cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest). Patients' electrolyte levels should be monitored as should symptoms of dysrhythmias.

Aminoglycosides
The ototoxic effects of aminoglycosides may be increased by concomitant administration of potent diuretics such as BURINEX.

Potassium depleting medicines
The potassium depleting effect of BURINEX may be increased by other potassium depleting medicines (see section 4.4 and 4.8).

Probenecid
Probenecid inhibits the renal tubular secretion of BURINEX leading to a diminished natriuresis.

4.6 Fertility, pregnancy and lactation
Pregnancy
The use of BURINEX in the first trimester of pregnancy should be avoided.

Breastfeeding
BURINEX should not be used during breastfeeding.

Fertility
No human data available.

4.7 Effects on ability to drive and use machines
BURINEX has no or negligible direct influence on the ability to drive and use machines. However, the patient should be informed that dizziness may occur during treatment and take this into account while driving or using machines.

4.8 Undesirable effects
Tabulated summary of adverse reactions
Undesirable effects are listed by MedDRA system organ class.

Blood and lymphatic system disorders	
Uncommon:	Bone marrow depression
Frequency not known:	Thrombocytopenia
Metabolism and nutrition disorders	
Frequency not known:	Fluid and electrolyte depletion, dehydration, (including hypokalaemia, hyponatraemia, hypochloraemia and hyperkalaemia, see sections 4.4 and 4.5), hyperuricaemia
Endocrine disorders	
Frequency not known:	Hyperglycaemia
Ear and labyrinth disorders	
Frequency not known:	Hearing disturbances (reversible)
Vascular disorders	
Frequency not known:	Hypotension
Gastrointestinal disorders	
Frequency not known:	Abdominal pain, vomiting, dyspepsia, diarrhoea, stomach cramps, nausea, pancreatitis (with high doses)
Hepato-biliary disorders	
Frequency not known:	Encephalopathy in patients with pre-existing hepatic disease, abnormalities of serum levels of hepatic enzymes
Skin and subcutaneous tissue disorders	
Frequency not known:	Skin rashes, pruritus, urticaria
Musculoskeletal and connective tissue disorders	
Frequency not known:	Arthralgia, muscular cramps in the legs, musculoskeletal pain sometimes associated with muscle spasm (with high doses)
Reproductive system and breast disorders	
Frequency not known:	Gynaecomastia and painful breasts
General disorders and administration site conditions	
Frequency not known:	Oedema
Investigations	
Frequency not known:	Raised blood urea and serum creatinine

For high dose therapy, treatment should be initiated at a low dose and gradually increased in 5 mg increments until the desired response is obtained.

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. Health care 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
Symptoms are those caused by excessive diuresis.

Generally, measures should be taken to restore blood volume, maintain blood pressure and correct electrolyte disturbance. No other specific treatment appears to be necessary.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
A 18.1 Diuretics
Pharmacotherapeutic group: Sulphonamides, plain, ATC code: C03CA 02

BURINEX (bumetanide) is a potent high ceiling diuretic, with a rapid onset and a short duration of action.

After oral administration, diuresis begins within thirty minutes with a peak effect between one and two hours. The diuretic effect is virtually complete in four to six hours.

The diuretic effect produced by BURINEX is dose related so that patients who fail to respond to a low dose may respond as the dose is increased. BURINEX has been shown to exert its major effect in the ascending limb of the loop of Henle, but it may also have an additional action in the proximal tubule. BURINEX is a derivative of metanilamide and is chemically distinct from other available diuretics.

Investigations in healthy volunteers as well as in patients have revealed that BURINEX is excreted in the urine.

5.2 Pharmacokinetic properties
Bumetanide is well absorbed after oral administration with bioavailability reaching between 80 and 95 %. The elimination half-life ranges from between 0,75 to 2,6 hours. No active metabolites are known. Renal excretion accounts for approximately half the clearance with hepatic excretion responsible for the other half. There is an increase in half-life and a reduced plasma clearance in the presence of renal or hepatic disease. In patients with chronic renal failure, the liver takes more importance as an excretory pathway although the duration of action is not markedly prolonged.

In neonates and infants, elimination appears slower than in older paediatric patients and adults, possibly because of immature renal and hepato-biliary functions. Mean serum elimination half-life decreases during the first month of life from 6 hours in neonates to 2.4 hours in infants 1 month of age.

Mean serum elimination half-life is 2.5 and 1.5 hours in infants younger than 2 months of age and in those 2–6 months of age, respectively. Data for younger children, including neonates and infants, is not sufficient to allow for dosing recommendations, see section 4.2.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Agar powder
Corn starch
Lactose
Magnesium stearate
Polyethyleneglycol sorbitan oleate
Polyvinylpyrrolidone
Silicon dioxide
Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.
Protect from light.
Keep blisters in the carton until required for use.

6.5 Nature and contents of container

BURINEX 1 mg tablets are packed in PVC/Aluminium blisters. Cartons containing three (3) or ten (10) blister packs of 10 tablets each.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

G/18.1/94

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06 December 1974

10. DATE OF REVISION OF THE TEXT

01 August 2022

Botswana: S2 B9300365

Namibia: NS2 05/18.1/0140