NEW ZEALAND DATA SHEET

1 NAME OF THE MEDICINE

Burinex® 1 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg of bumetanide (i.e. 3-n-(butylamino)-4-phenoxy-5-sulphamoyl-benzoic acid).

Excipients with known effect:
Lactose monohydrate (see Section 4.4 Special warnings and precautions for use)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Burinex® 1 mg tablets are white, round flat, circular (diameter 8 mm), uncoated with a bevelled edge, and are marked on one face with a score line and the number “133”.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Burinex® is indicated for the treatment of oedema, particularly that associated with congestive heart failure, hepatic and renal diseases including the nephrotic syndrome and acute pulmonary oedema.

4.2 Dose and method of administration

Oral administration

Most patients will respond to 1 mg daily, administered as a single dose, either in the morning or early evening.

If the diuretic response to an initial dose of Burinex® is not adequate, and in view of its rapid onset and short duration of action, a second or third dose may be given at 4 to 5 hour intervals up to a maximum daily dose of 10 mg in refractory patients. An intermittent dose schedule, whereby Burinex® is given on alternate days or for 3 to 4 days with rest periods of 1 to 2 days in between, is recommended as the safest and most effective method for the continued control of oedema.

4.3 Contraindications

1. Anuria: Although Burinex® can be used to induce diuresis in renal insufficiency, any marked increase in blood urea nitrogen or creatinine or the development of oliguria during therapy of patients with progressive renal disease is an indication for the discontinuation of treatment with Burinex®.
2. Hepatic encephaolopathy including coma.
3. Severe electrolyte depletion.
4. Hypersensitivity to active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS), which can be life-threatening or fatal, have been reported in relation to non-antibiotic sulphonamide containing products, including bumetanide. Patients should be advised of the signs and symptoms of SJS and TEN and closely monitored for those. If signs and symptoms suggestive of these reactions appear, bumetanide should be withdrawn, and an alternative therapy should be considered. If the patient has developed a serious reaction such as SJS or TEN, with the use of bumetanide, treatment with bumetanide must not be restarted in this patient at any time.

Excessive doses or too-frequent administration can lead to profound water loss, electrolyte depletion, dehydration, reduction in blood volume and circulatory collapse with the possibility of vascular thrombosis and embolism, particularly in elderly patients.

Periodic determinations of other electrolytes (in particular, sodium, potassium, chloride, calcium and bicarbonate) are advised in patients treated with high doses or for prolonged periods, particularly in those on low salt diets.

Electrolyte and fluid imbalance may occur, and replacement therapy should be instituted where indicated. Serum potassium concentrations should be monitored regularly.

As with other diuretics, bumetanide may cause an increase in blood uric acid. Reversible elevations of blood urea nitrogen (BUN) and creatinine may also occur, especially in association with dehydration and in patients with renal failure.

Caution is advised if bumetanide is to be administered to patients with severe or progressive renal impairment or with elevated urea/Blood Urea Nitrogen (BUN) or creatinine.

Caution is advised if bumetanide is to be administered to patients with severe hepatic impairment.

Special caution should be used in these conditions since sudden changes in electrolyte balance may precipitate hepatic encephalopathy and coma.

If known hypersensitivity to sulphonamides there may be a potential risk of hypersensitivity to bumetanide.

The possibility of an effect on glucose metabolism exists. Periodic monitoring of urine and blood glucose should be made in diabetics and patients suspected of latent diabetes.

Bumetanide should be used with care in patients with prostatic hypertrophy or impairment of micturition.

Bumetanide should be used with caution in patients with potential obstruction of the urinary tract.

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

Bumetanide found in urine by doping test is cause for disqualification of athletes.

Administration of proton pump inhibitors has been associated with development of hypomagnesaemia, Hypomagnesaemia may be exacerbated with co-administration of Burinex® and particular attention to magnesium levels should be given when this combination is used.

Burinex® tablets contains lactose as an excipient and patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Paediatric population:

Safety and efficacy in children below the age of 18 years has not been established.

4.5 Interaction with other medicines and other forms of interaction

Lithium
Burinex® should not be administered concurrently with lithium salts since diuretics can reduce lithium clearance, resulting in high serum levels of lithium.

Probenecid
The diuretic and natriuretic effects of bumetanide are inhibited by probenecid.

Antihypertensive agents and medicinal products inducing postural hypotension.
Bumetanide may potentiate the effect of antihypertensive drugs including diuretics and drugs inducing postural hypotension (e.g. tricyclic antidepressants), necessitating a reduction in the dosage of the antihypertensive. First-dose hypotension may occur.

Digitalis glycosides
Hypokalaemia increases the sensitivity to digitalis glycosides which might result in digitalis toxicity (nausea, vomiting and arrhythmias). Potassium level and signs for digitalis toxicity should be monitored. Potassium supplementation and lower digitalis glycoside dose should be considered.

Drugs with ototoxic potential
Animal studies have shown bumetanide may produce ototoxicity.
The possibility of ototoxic potentiation in humans cannot be excluded and concomitant administration of bumetanide and ototoxic drugs such as aminoglycosides should be avoided. This is of particular importance when renal function is impaired. It has been suggested that bumetanide may cause significantly less ototoxicity than frusemide.

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

Drugs with nephrotoxic potential
There has been no experience on the concurrent use of Burinex® with drugs known to have a nephrotoxic potential. Therefore, the simultaneous administration of these drugs should be avoided.

Anticoagulants
Interaction studies in humans have shown Burinex® to have no effect on warfarin metabolism or on plasma prothrombin activity.

Non-depolarising neuromuscular blocking agents
Hypokalaemia increases the sensitivity to non-depolarising neuromuscular blocking agents.

Antiarrhythmics
Concomitant use of bumetanide and class III antiarrhythmic drugs 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 arrhythmias.

NSAIDs
Non-steroidal anti-inflammatory drugs (NSAID) inhibit the effect of bumetanide. The effects of concurrent use should be monitored (e.g. blood pressure, signs of renal failure). Diuretics may enhance the nephrotoxicity of NSAIDs.
Indomethacin may decrease the effect of bumetanide.

Potassium depleting agents
The potassium depleting effect of bumetanide may be increased by other potassium depleting agents.

4.6 Fertility, pregnancy and lactation

Pregnancy: Category C

Bumetanide may cause harmful pharmacological effects during pregnancy, to the foetus or to the newborn child. Burinex® should not be used during pregnancy unless the expected benefits outweigh the potential risks.

Breast-feeding
Bumetanide should not be used during breastfeeding.

Fertility
There are no clinical studies with Bumetanide regarding fertility.

4.7 Effects on ability to drive and use machines

Bumetanide 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

The estimation of the frequency of undesirable effects is based on a pooled analysis of data from clinical studies and spontaneous reporting.
Based on pooled data from clinical studies including more than 1000 patients who received bumetanide, approximately 12 % of patients can be expected to experience an undesirable effect.
The most frequently reported adverse reactions during treatment are headache and electrolyte imbalance (including hypokalaemia, hyponatraemia, hypochloraemia and hyperkalaemia) occurring in approximately 4% of the patients, followed by dizziness (including orthostatic hypotension and vertigo) and fatigue occurring in approximately 3% of patients.
Encephalopathy (in patients with pre-existing liver disease), ECG changes, hives, arthritic pain can occur. Manifestations of the pharmacologic activity, such as increased serum creatinine and BUN, and azotemia may occur, particularly during intensive or prolonged therapy. Blood dyscrasias, liver damage, idiosyncratic reactions and gynaecomastia have been reported.

Electrolyte disturbances can occur especially during long term treatment.

Renal failure has been reported in post-marketing safety surveillance.

Undesirable effects are listed by MedDRA system organ class (SOC) and the individual undesirable effects are listed starting with the most frequently reported. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Very common: ≥1/10
Common: ≥1/100 and < 1/10
Uncommon: ≥1/1,000 and <1/100
Rare: ≥1/10,000 and <1/1,000
Very rare <1/10,000
Not known: frequency cannot be estimated from the available data

Blood and lymphatic system disorders	
Uncommon (≥1/1,000 and <1/100)	Bone marrow failure and pancytopenia Thrombocytopenia Leukopenia including neutropenia Anaemia
Metabolism and nutrition disorders	
Common: (≥1/100 and < 1/10)	Electrolyte imbalance (including hypokalaemia, hyponatraemia, hypochloraemia and hyperkalaemia)
Uncommon: (≥1/1,000 and <1/100)	Dehydration Glucose metabolism disorder Hyperuricaemia and gout
Nervous system disorders	
Common: (≥1/100 and < 1/10)	Dizziness (including orthostatic hypotension and vertigo) Fatigue (including lethargy, somnolence, asthenia and malaise) Headache
Uncommon: (≥1/1,000 and <1/100)	Syncope
Ear and labyrinth disorders	
Uncommon: (≥1/1,000 and <1/100)	Hearing disturbances
Cardiac disorders	
Uncommon: (≥1/1,000 and <1/100)	Chest pain and discomfort
Vascular disorders	
Uncommon: (≥1/1,000 and <1/100)	Hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon: (≥1/1,000 and <1/100)	Dyspnoea Cough
Gastrointestinal disorders	
Common: (≥1/100 and < 1/10)	Abdominal pain and discomfort Nausea
Uncommon: (≥1/1,000 and <1/100)	Vomiting Diarrhoea Constipation Dry mouth and thirst

Skin and subcutaneous tissue disorders	
Uncommon: (≥1/1,000 and <1/100)	Rash* Dermatitis and eczema Urticaria Pruritus Photosensitivity *Various types of rash reactions such as erythematous, maculo-papular and pustular have been reported
Not known : (frequency cannot be estimated form available data)	Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (see section 4.4)
Musculoskeletal and connective tissue disorders	
Common: (≥1/100 and < 1/10)	Muscle spasms Pain and myalgia
Renal and urinary disorders	
Common: (≥1/100 and < 1/10)	Micturition disorder
Uncommon: (≥1/1,000 and <1/100)	Renal impairment (including renal failure)
General disorders and administration site conditions	
Uncommon: (≥1/1,000 and <1/100)	Oedema peripheral

In one study, increased serum amylase values were observed in 4 out of 11 patients. The cause of this is unknown, but could be due to subclinical pancreatitis with some extrahepatic cholestasis.

Other clinical adverse reactions, which have each occurred in approximately 0.1% of patients, are ear discomfort, sweating, hyperventilation, itching, nipple tenderness, premature ejaculation and difficulty maintaining an erection.

Laboratory abnormalities reported have included hyperuricaemia (in 18.4% of patients tested), hypochloremia (14.9%), hypokalaemia (14.7%), azotemia (10.6%), hyponatraemia (9.2%), increased serum creatinine (7.4%), hyperglycaemia (6.6%) and variations in phosphorus (4.5%). CO2 content (4.3%), bicarbonate (3.1%) and calcium (2.4%). Although manifestations of the pharmacologic action of bumetanide, these conditions may become more pronounced by intensive therapy.

Diuresis induced by bumetanide may also rarely be accompanied by changes in LDH (1.0%), total serum bilirubin (0.8%), serum proteins (0.7%), AST (0.6%), SGPT (0.5%), alkaline phosphatase (0.4%), cholesterol (0.4%) and creatinine clearance (0.3%). Also reported have been deviations in haemoglobin (0.8%), prothrombin time (0.8%), haematocrit (0.6%), WBC (0.3%) platelet counts (0.2%) and differential counts

(0.1%). Increases in urinary glucose (0.7%) and urinary protein (0.3%) have also been seen.

Reporting of suspected adverse reactions
Reporting suspected adverse reaction after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose
In high doses and during long-term treatment loop diuretics may cause electrolyte imbalance, polyuria and dehydration. Further overdose can lead to reduction of blood volume and circulatory collapse with a possibility of vascular thrombosis and embolism.
Symptoms of electrolyte imbalance include dry mouth, thirst, weakness, lethargy, drowsiness, mental confusion, gastrointestinal disturbances, restlessness, muscle pain, cramps, seizures, anorexia and vomiting.
Symptoms of dehydration include dizziness, postural hypotension, postural tachycardia. With large and acute fluid losses hypovolemic shock may occur, manifest as hypotension, tachycardia, peripheral vasoconstriction, and hypoperfusion with cyanosis, cold and clammy extremities, oliguria, and altered mental status

Treatment is by adjustment of the fluid and electrolyte imbalance.

Contact the NZ National Poison Centre on 0800 764 766 for further advice on overdose management.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Burinex® is a loop diuretic with a rapid onset and short duration of action. Pharmacological and clinical studies have shown that 1 mg bumetanide has a diuretic efficacy equivalent to approximately 40 mg frusemide. The major site of action is the ascending limb of the loop of Henle where it inhibits sodium reabsorption.

Reabsorption of chloride in the ascending loop is also blocked by bumetanide. The excretion of chloride is greater than that of sodium and bumetanide also increases potassium excretion in a dose-related fashion. Bumetanide decreases uric acid excretion and increases serum uric acid. Bumetanide may have an additional action on the proximal tubule. This proximal tubular activity does not seem to be related to an inhibition of carbonic anhydrase. Bumetanide does not exert an observable effect on the distal tubule. The diuretic effect of bumetanide is dose-related so that patients who fail to respond to a low initial dose usually respond as the dose is increased.

5.2 Pharmacokinetic properties

After oral administration, diuresis begins within 30 minutes with a peak effect between 1 and 2 hours. At

usual doses (1–2 mg) the diuretic effect is virtually complete in 3–4 hours. After higher doses (3–5 mg) the diuretic action lasts for 4-6 hours. This short and rapid action minimises disturbance of the patient's daily routine.

Maximum plasma concentrations range between 30 ng/mL (80 nmoles/L) after administration of 1 mg, to 420 ng/mL (1150 nmoles/L) after 5 mg.

Absorption
Bumetanide is rapidly and almost completely absorbed when given orally.

Distribution
The apparent volume of distribution is approximately 25 L indicating that the drug is not distributed into tissues to any great extent. The degree of plasma protein binding is approximately 95%.

Metabolism and excretion
Approximately 75–80% of an administered dose is excreted in the urine within 48 hours, approximately 50% of the dose as the unchanged drug. Metabolism occurs by oxidation of the N-butyl side chain to form alcohol metabolites. These are excreted in the urine and bile mainly as glucuronides. Approximately 10% of the dose is excreted in the faeces. Bumetanide is eliminated rapidly with a plasma half-life of 60–90 minutes.

The similar fate of bumetanide following intravenous and oral administration excludes the possibility of any significant first pass effect or degradation in the gastro-intestinal tract.

6 PHARMACEUTICAL PARTICULARS

Bumetanide is a derivative of metanilamide, and is therefore structurally different to frusemide and the thiazides which are derivatives of sulphanilamide. It is a white odourless crystalline powder with a slightly bitter taste. It melts at approximately 230°C and at 22°C is soluble in ethanol and acetone; slightly soluble in ether and chloroform, very slightly soluble in water and practically insoluble in hydrochloric acid. It should be protected from light.

The molecular weight is 364.41

6.1 Excipients
Bumetanide® Tablets contains agar, copovidone, hydrated silica, lactose monohydrate, magnesium stearate, maize starch, polysorbate 80 and purified talc.

6.2 Incompatibilities
Not applicable.

6.3 Shelf-life
2 years from date of manufacture.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

Burinex® 1 mg tablets are presented in blister packs of 100.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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21 August 2024

Summary table of changes

Section changed	Summary of new information
4.4 and 4.8	Safety update