

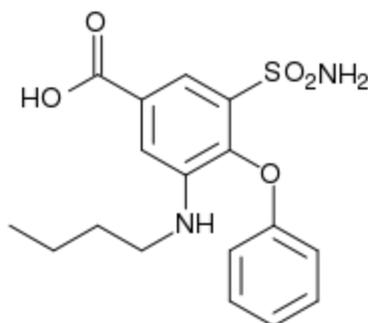
BURINEX[®] PRODUCT INFORMATION

(bumetanide)

NAME OF THE MEDICINE

Burinex[®] 1 mg tablets contain bumetanide i.e.
3-n-(butylamino)-4-phenoxy-5-sulphamoyl-benzoic acid.

The structural formula of bumetanide is:



The CAS registry number is 28395-03-1.

DESCRIPTION

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.

PHARMACOLOGY

Pharmacodynamics

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.

Pharmacokinetics

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.

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.

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 discontinuation of treatment with Burinex[®].
2. Patients in hepatic coma or in states of severe electrolyte depletion until the condition is improved or corrected.
3. Patients hypersensitive to bumetanide. Reports of successful treatment with Burinex[®] following instances of allergic reactions to frusemide suggests a lack of cross-sensitivity between the two substances.

PRECAUTIONS

1. Volume and electrolyte depletion

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.

Serum potassium should be measured periodically and potassium supplements or potassium-sparing diuretics added if necessary. Prevention of hypokalaemia is of particular importance in patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis or ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, certain diarrhoeal states, or other states where hypokalemia is thought to represent particular added risks to the patient, i.e. history of ventricular arrhythmias.

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.

Symptoms of electrolyte depletion are weakness, dizziness, lethargy, leg cramps, anorexia, vomiting or mental confusion.

Asymptomatic hyperuricaemia may occur. Reversible elevations of blood urea nitrogen (BUN) and creatinine may also occur, especially in association with dehydration and in patients with renal failure.

2. Hepatic cirrhosis and ascites

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

3. Allergy to sulphonamides

Patients allergic to sulphonamides may also exhibit hypersensitivity to bumetanide.

4. Glucose metabolism

Studies in normal subjects receiving Burinex[®] revealed no adverse effects on glucose tolerance, plasma insulin, glucagon and growth hormone levels, but the possibility of an effect on glucose metabolism exists. Periodic determinations of blood sugar should be made, particularly in patients with diabetes or suspected latent diabetes.

5. Genito-urinary conditions

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

6. Use in pregnancy: Category C

Thiazides, related diuretics and loop diuretics enter the foetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has been reported with thiazides and related diuretics. Loop diuretics like frusemide and bumetanide are also associated with this risk. During the latter part of pregnancy products of this type should therefore only be given on sound indications, and then the lowest effective dose. Bumetanide has not been shown to be teratogenic in animal testing. However as for all drugs, it should only be administered during the first trimester of pregnancy if the expected benefits outweigh the potential risks.

7. Use in lactation

It is not known whether bumetanide is excreted in breast milk, therefore the drug is not recommended for use during lactation unless the expected benefits outweigh the potential risks.

8. Paediatrics

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

INTERACTIONS WITH OTHER MEDICINES

1. Lithium

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

2. Probenecid

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

3. Antihypertensives

Bumetanide may potentiate the effect of various antihypertensive drugs, necessitating a reduction in the dosage of the antihypertensive.

4. Digitalis

Low serum potassium levels may increase the sensitivity of the myocardium to the toxic effects of digitalis preparations, however studies have shown no direct effect of bumetanide on digoxin blood levels.

5. 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.

6. 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.

7. Anticoagulants

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

8. Indomethacin

Indomethacin may decrease the effect of bumetanide.

ADVERSE EFFECTS

Most frequent

Muscle cramps (severe with higher doses), dizziness, headache and nausea, hypotension, encephalopathy (in patients with pre-existing liver disease) and fluid and electrolyte imbalance.

Less frequent

Impaired hearing, rash, pruritus, ECG changes, weakness, hives, abdominal pain, arthritic pain, musculoskeletal pain, vomiting.

Manifestations of the pharmacologic activity, such as increased serum creatinine and BUN, hyperuricaemia and azotemia may occur, particularly during intensive or prolonged therapy.

Blood dyscrasias (including leucopenia and thrombocytopenia), liver damage, idiosyncratic reactions and gynaecomastia have been reported.

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 vertigo, chest pain, ear discomfort, fatigue, dehydration, sweating, hyperventilation, dry mouth, upset stomach, renal failure, asterixis, itching, nipple tenderness, diarrhoea, 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.

DOSAGE AND 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.

OVERDOSAGE

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

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

Symptomatic treatment. Adjustment of the fluid and electrolyte imbalance by careful monitoring of urine and electrolyte output and serum electrolyte levels should be carried out. General measures should be taken to restore blood volume, maintain blood pressure and correct electrolyte disturbances.

Contact the Poisons Information Centre on 131 126 for further advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

Burinex[®] 1 mg tablets are white, circular (diameter 8 mm), with a bevelled edge, and are marked on one face with a score line and the number 133, and with an Assyrian Lion on the other face.

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

Store below 25°C. Keep the blister in the carton in order to protect from light.

NAME AND ADDRESS OF SPONSOR

CSL Limited
ABN 99 051 588 348
45 Poplar Rd
Parkville VIC 3052
Australia

POISON SCHEDULE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

23 July 1987

DATE OF MOST RECENT AMENDMENT

27 January 2015

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