1. NAME OF THE MEDICINAL PRODUCT

Burinex® Tablet

Bumetanide

Carefully read this insert before administering this product. It contains information about your treatment. If you have any doubt or you are not sure about something, please ask your physician or Pharmacist chemist.
Keep this insert as you might need to read it again.
Verify this product fully corresponds to the one prescribed by your physician.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets:
Bumetanide 1 mg
Pack sizes: 10, 20, 30, 50 and 100 tablets

Excipients the clinician should be aware of:
Lactose

For the full list of excipients, see section 6.1.

Not all pack sizes, strengths and formulations may be marketed

Sale under prescription

3. PHARMACEUTICAL FORM

Tablets:
1 mg:
White, circular, flat tablets embossed with the number 133 on one side.

The tablets have a score line.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Burinex® is indicated whenever diuretic therapy is required in the treatment of oedema *e.g.* associated with congestive heart failure, cirrhosis of the liver, renal diseases including the nephrotic syndrome. Acute pulmonary oedema, drug induced fluid retention, and drug poisoning that can be treated by forced diuresis. Hypertension.

4.2 Posology and method of administration

Orally: 1 mg daily.
In refractory cases the dose can be increased gradually till a satisfactory response has been obtained. Rarely will it be necessary to exceed a dose of 4 mg daily. In high dose therapy consideration should be given to a twice daily dosing.
Children: The dose is calculated on the basis of 0.03–0.06 mg/kg daily.
Elderly: Adjust dosage according to response; a dose of 0.5 mg daily may be sufficient in some elderly patients.
Where intramuscular administration is considered appropriate a dose of 1 mg should be given initially and the dose then be adjusted according to the diuretic response.

4.3 Contraindications

For Burinex® Tablets:
- Hypersensitivity to active substance or to any of the excipients
- Severe electrolyte depletion
- Persisting anuria
- Hepatic encephalopathy including coma

4.4 Special warnings and precautions for use

For Burinex® Tablets:
Caution is advised if bumetanide is to be administered to patients with severe hepatic impairment. Caution should be exercised when bumetanide is used in patients with hypotension. Electrolyte and fluid imbalance may occur (see section 4.8) and replacement therapy should be instituted where indicated. Serum potassium concentrations should be monitored regularly.

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.

As with other diuretics, bumetanide may cause an increase in blood uric acid. Bumetanide should be used with caution in patients with potential obstruction of the urinary tract.

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.
Periodic monitoring of urine and blood glucose should be made in diabetics and patients suspected of latent diabetes.
If known hypersensitivity to sulphonamides there may be a potential risk of hypersensitivity to bumetanide.
Bumetanide found in urine by doping test is cause for disqualification of athletes.
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.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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

Lithium
Bumetanide reduces lithium clearance resulting in high serum levels of lithium, therefore concomitant therapy requires close monitoring of serum lithium levels. Lower lithium doses may be required.

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.

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

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
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 clinical condition of the woman requires treatment with bumetanide. It may be used only in case of heart failure when the potential benefit justifies the potential risk to the foetus.

Breastfeeding
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.

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

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
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

Paediatric population
The safety profile of Burinex® has not been established in the paediatric population.

4.9 Overdose
In high doses and during long-term treatment loop diuretics may cause electrolyte imbalance, dehydration and polyuria.

Symptoms of electrolyte imbalance include dry mouth, thirst, weakness, lethargy, drowsiness, confusion, gastrointestinal disturbances, restlessness, muscle pain and cramps and seizures.

Treatment is by adjustment of the fluid and electrolyte imbalance.

5. PHARMACOLOGICAL PROPERTIES

5.0 Therapeutic classification
C 03 CA 02 - Sulfonamides, plain

5.1 Pharmacodynamic properties
Bumetanide is a potent high ceiling loop diuretic.
Bumetanide exerts an inhibiting effect on the reabsorption mechanism of salts in the thick ascending limb of Henle and in the renal proximal tubules.
Bumetanide hereby exerts a diuretic and natriuretic action.

5.2 Pharmacokinetic properties
Tablets:
Bumetanide is nearly totally absorbed from the gastro-intestinal tract.After peroral administration, bioavailability of between 80-90% is observed. More than 90% is protein bound. Diuresis begins within 1/2-1 hour with a peak effect between one and two hours. The diuretic effect lasts up to about 4 hours after oral administration of a dose of 0.5 – 1 mg. Bumetanide is eliminated with a half-life between 1 to 2 hours after oral administration. It is strongly bound to plasma proteins and renal excretion accounts for about half of the total clearance. The hepatic metabolism and biliary excretion accounts for the other half. The primary metabolites are conjugated alcohols of bumetanide. No active metabolites have been found. Burinex has a steep dose response curve.

5.3 Preclinical safety data
Bumetanide has shown no mutagenic, teratogenic or carcinogenic effects in the preclinical studies although data from investigative preclinical studies *in vitro* and *in vivo* suggest a possible effect on pre- and postnatal kidney, lung and neurogenic development. Non-clinical data reveal no special hazard for humans at the recommended therapeutic dose based on conventional studies of acute, subacute and repeated dose toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablets:
- Agar
- Lactose monohydrate
- Povidone
- Magnesium stearate
- Maize starch
- Polysorbate 80
- Colloidal anhydrous silica
- Talc

6.2 Shelf life
Tablets:
1 mg: 3 years.

6.3 Special precautions for storage
Tablets:
1 mg: store below 30°C.
Keep the blister in the outer carton to protect from light.

Keep medicines out of reach of children.

6.4 Nature and contents of container
Blister pack consisting of polyvinyl chloride on aluminium foil.

Pack sizes: 100 tablets

7. MANUFACTURER

Tablets:
allphamed PHARBIL Arzneimittel GmbH
Hildebrandstr. 10-12
Göttingen, Niedersachsen, 37081
Germany

For

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