SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Burinex Tablets 5mg/ Burinex Tablets 1mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bumetanide, 1 mg
Excipient with known effect: Each tablet contains 52.3 mg lactose monohydrate.

Bumetanide, 5 mg
Excipient with known effect: Each tablet contains 92.0 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Tablet characteristics:
1 mg:
White, circular, flat tablets embossed with the number 133 on one side.
The tablet can be divided into equal doses.

5 mg:
White, flat, circular (10 mm), uncoated bevelled edge tablet marked on one face with a score line and "5 mg". The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Burinex 1 mg Tablets are indicated for the treatment of oedema due to congestive heart failure, cirrhosis of the liver and renal disease including nephrotic syndrome in adults.

Burinex 5 mg Tablets are indicated for the treatment of renal, hepatic or cardiac oedema in adults when high doses of a potent, short-acting diuretic is required.

4.2 Posology and method of administration

Posology
1 mg:
The dose should be titrated in each patient according to the patients' response and the required therapeutic activity.
In most patients, initial dose is 0.5-1 mg daily. The dose may be increased to 2 mg 2-3 times daily until a satisfactory diuretic response is obtained.

5 mg:
The dose should be carefully titrated for each patient on the basis of the desired therapeutic effect and the response obtained. As a general rule for patients who are not under control with a low dose, a starting dose of

5 mg can be applied, and if necessary, it can be gradually increased until a satisfactory response is obtained or adverse effects appear. A twice daily dosing regimen instead of once daily, can be preferentially considered.

Paediatric population
This medicinal product is not recommended for children as there is limited information on the safety, efficacy and dosage in children.

Elderly
The dosage recommendations for adults apply, however in the elderly, bumetanide is generally eliminated more slowly. Dosage should be titrated until the required response is achieved.

Patients with liver or renal insufficiency
Bumetanide is excreted partly via the kidneys and partly via hepatic metabolism and biliary excretion. The dose should be titrated according to the patient's response and required therapeutic effect (see section 4.4).

Method of administration
Burinex Tablets are for oral use. The bioavailability is not affected by food intake.

4.3 Contraindications

- Hypersensitivity to bumetanide or to any of the excipients listed in section 6.1
- Severe electrolyte depletion
- Persisting anuria
- Hepatic encephalopathy including coma

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.

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

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

Electrolyte imbalance
Electrolyte imbalance may occur (see section 4.8) and replacement therapy should be instituted where indicated. Serum potassium concentrations should be monitored regularly.

Proton Pump Inhibitors
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.

Hyperuricaemia
As with other diuretics, bumetanide may cause an increase in blood uric acid.

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

Renal Impairment

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.

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

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

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

Excipient warning
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 concomi- tant 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.
Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Breast-feeding
It is unknown whether bumetanide/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Burinex.
Bumetanide should not be used during breast-feeding.

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.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), have been reported in association with bumetanide (see section 4.4).

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 (cannot be estimated from the available data)

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

	*Various types of rash reactions such as erythematous, maculo-papular and pustular have been reported
Not known	Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	
Common:	Muscle spasms Pain and myalgia
Renal and urinary disorders	
Common:	Micturition disorder
Uncommon:	Renal impairment (including renal failure)
General disorders and administration site conditions	
Uncommon:	Oedema peripheral

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via ADR Reporting:
Website: www.medicinesauthority.gov.mt/adrportal

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 adjustment of the fluid and electrolyte imbalance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sulphonamides, plain, ATC code: C03CA 02

Bumetanide is a potent high-ceiling loop diuretic.

Bumetanide exerts an inhibiting effect on the reabsorption mechanism of salts in the ascending limb of the loop of Henle and in the renal proximal tubuli. Bumetanide thereby causes the diuretic and natriuretic action observed.

5.2 Pharmacokinetic properties

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.
In neonates and infants, elimination appears slower than in older paediatric patients and adults, possibly because of immature renal and hepatobiliary 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. The apparent elimination half-life may be prolonged to approximately 6 hours (with a range up to 15 hours) after IV administration in premature or full-term neonates with respiratory disorders. Data for younger children, including neonates and infants, is not sufficient to allow for dosing recommendations, see 4.2.

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

Maize starch, lactose monohydrate, povidone, polysorbate 80, colloid anhydrous silica, agar powder, talc, magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep the blister in the outer carton in order to protect from light.
1 mg: Store below 30 °C.
5 mg: Store below 25 °C

6.5 Nature and contents of container

Blister packs consisting of PVC sealed on aluminium foil.
1 mg: Pack size of 100 tablets
5 mg: Pack size of 20 and 100 tablets

6.6 Special precautions for disposal

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Karo Pharma AB
Box 16184
103 24 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

1 mg: MA1303/00101
5 mg: MA1303/00103

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1 mg: 1st November 2006
5 mg: 11th July 2022

10. DATE OF REVISION OF THE TEXT

November 2024