Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Burinex 1 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg of Bumetanide.

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
A white, flat, circular, uncoated scored tablet marked with the number 133 on the scored face.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Posology

The usual daily dosage is 0.5 to 2 mg as a single or divided dose. The dosage may be increased if necessary and should be carefully adjusted according to patient response.

Paediatric population

The medicinal product is not recommended for children as there is limited information on safety, efficacy and dosage in children.

Elderly

The dosage recommendations for adults apply, but 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

Depending on the liver or renal function, the dose should be titrated according to the patient's response and required therapeutic effect (see section 4.4).

Method of administration

For oral administration.

4.3 Contraindications

Hypersensitivity to the active substance 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

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

Hypomagnesaemia
Administration of proton pump inhibitors has been associated with development of hypomagnesaemia. Hypomagnesaemia may be exacerbated with co-administration of bumetanide 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
In patients with severe chronic renal failure treated with high doses of bumetanide, there have been reports of severe generalised musculoskeletal pain sometimes associated with muscle spasm, occurring one or two hours after administration and lasting for up to 12 hours. Occasionally analgesic medication has been required to treat the pain. All patients recovered fully and there was no deterioration in their renal function. The cause of this pain is uncertain but may be a result of varying electrolyte gradients at the cell membrane level. Experience suggests that the incidence of such reactions is reduced by initiating treatment at 5-10 mg daily and titrating upwards, using a twice daily dosage regimen at doses of 20 mg per day or more. When using more than 10 mg per day expert advice should be sought. Patients with chronic renal failure on high doses of bumetanide should remain under constant hospital supervision.

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 of urine and blood glucose should be made in diabetics and patients suspected of latent diabetes since this preparation may induce hyperglycaemia (see sections 4.5 and 4.8).

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

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

Excipients warning
Burinex tablets contain 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 interactions

Dose adjustment of hypoglycaemic agents 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 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. Bumetanide 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.

Breast-feeding
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, approximately12% 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, hypochloraemiaandhyperkalaemia) occurring in approximately 4% ofthe patients, followed bydizziness (including orthostatic hypotension and vertigo) and fatigue occurring in approximately3 % of patients.

Electrolyte disturbances can occur especially during long term treatment.
Renal failure has been reported in post-marketing safety surveillance.
Undesirable effectsarelisted by Med DRA 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
Earand labyrinth disorders	
Uncommon: (≥1/1,000 and <1/100)	Hearing disturbances
Cardiac disorders	
Uncommon (≥1/1,000 and <1/100)	Chest pain and discomfort
Vasculardisorders	
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 Drymouth 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 Bumetanide 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL- Dublin 2;Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 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 tubules. 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, a bioavailability of between 80-95% is observed. Diuresis begins within ½-1 hour with a peak effect between 1 and 2 hours. The diuretic effect lasts up to about 4 hours. Bumetanide is eliminated with half-life ranging from between 1 to 2 hours after oral administration of a dose of 0.5-2 mg. It is strongly bound to plasma proteins and renal excretion of unchanged drug 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. Bumetanide 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

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Lactose monohydrate
Povidone
Polysorbate 80
Colloidal 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 blisters in the outer carton in order to protect from light.
Store below 30°C.

6.5 Nature and contents of container

PVC/aluminium blister packs of 14 (physician's sample), 30 and 56 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

PA22650/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1978

Date of latest renewal: 01 April 2008

10 DATE OF REVISION OF THE TEXT

October 2020