SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Burinex 0.5 mg/ml, solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Burinex ampoule contains 0.5 mg bumetanide per millilitre.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Burinex 0.5 mg/ml, solution for injection is indicated in the management of acute oedema due to congestive heart failure, including pulmonary oedema, cirrhosis of the liver and renal disease including nephrotic syndrome in adults. Drug intoxication where forced diuresis is desirable in adults.

4.2 Posology and method of administration

Posology
If oral administration is not feasible, of if a rapid effect is desired, bumetanide may be administered intramuscularly or intravenously. Usual dose is 0.5-1 mg.

Pulmonary oedema:
In less serious cases 0.5 mg intravenously. Repeat, if necessary, after 20 minutes. In acute cases 2 mg intravenously. Repeat, if necessary, 2 to 3 times at 20 minute intervals.

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

Elderly
Due to changed pharmaco-kinetics and pharmaco-dynamics the diuretic effect may decrease in elderly, increasing the risk of side effects. Therefore, the dosage must be determined in accordance with the efficiency and any adverse reactions to the medicinal product.

Patients with hepatic or renal impairment
Due to changed pharmaco-kinetics and/or pharmaco-dynamics the diuretic effect may decrease in patients with hepatic or renal insufficiency, increasing the risk of side effects. Therefore, the dosage must be determined in accordance with the efficiency and any adverse reactions to the medicinal product.

Renal impairment:

2-5 mg, repeat, if necessary, every 6 to 8 hours, or 2-5 mg in 500 ml solution for infusion administered over 30 to 60 minutes. Repeat, if necessary, every 6 to 8 hours.

Drug intoxication with salicylates or barbiturates:
2 mg intravenously as starting dose; then 1 mg every 4 hours up to a total of 7 mg daily. The usual procedure for increased alkaline diuresis must be followed. When intravenous infusion is required, bumetanide solution for injection may be added to the usual solution for injection, which is based on glucose, NaCl, NaHCO3 and KCl, as the maximum amount of bumetanide to be added is 10 mg bumetanide per 100 ml solution for infusion.

4.3 Contraindications

- Hypersensitivity to the active substance, formaldehyde (see Section 4.4) or to any of the excipients listed in section 6.1.
- Serious electrolyte depletion.
- Persisting anuria.
- Hepatic encephalopathy including coma.

4.4 Special warnings and precautions for use

Formaldehyde is a degradation product which occurs in the product in trace amounts during storage.
Due to the anaphylactic potential of formaldehyde, caution should be taken.

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 and 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.

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 of 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 is cause for disqualification of athletes.

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 new-born 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 new-borns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Burinex.
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.

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, <1/10
Uncommon ≥1/1,000, <1/100
Rare ≥1/10,000, <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 by 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 with rapid and short-term effect. Pharmacological and clinical tests show that the diuretic effect of 1 mg bumetanide corresponds to approx. 40 mg furosemide. However, differences in individual reactions should be taken into account. The diuretic effect of bumetanide is dose-dependent. Patients, who do not react to a low starting dose, usually react to an increased dose. Bumetanide is shown to have the largest effect on the proximal part of the loop of Henle, but may also have a supplementary effect in the proximal tubule.

5.2 Pharmacokinetic properties

After intravenous administration, diuresis occurs within a few minutes and usually ceases after approx. 2 hours. Bumetanide is eliminated with a half-life between 1 to 2 hours. In patients with hepatic or renal diseases the elimination half-life is prolonged. Bumetanide 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. 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 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

Xylitol, disodium hydrogen phosphate, sodium dihydrogen phosphate, water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C.
Store the ampoules in the outer packaging to protect against light.

6.5 Nature and contents of container

Ampoules (made of amber glass):	Carton box of 5 ampoules containing 2 ml each
	Carton box of 5 ampoules containing 4 ml each
	Carton box of 5 ampoules containing 10 ml each

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No particular 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)

MA1303/00102

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23rd November 2012/ 23th November 2017

10. DATE OF REVISION OF THE TEXT

November 24