PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrBURINEX®

Bumetanide Tablets

Tablets, 1 and 5 mg, Oral

Manufacturer's Standard

Diuretic

Karo Pharma AB
Box 16184
SE-103 24 Stockholm
Sweden

Date of Initial Approval:
July 19, 2022

Importer / Distributor
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Submission Control No: 263610

RECENT MAJOR LABEL CHANGES

Not applicable.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

BURINEX (bumetanide) is indicated for:

- The treatment of edema associated with congestive heart failure, cirrhosis of the liver and renal disease including the nephrotic syndrome.

1.1 Pediatrics

Pediatrics <18 years: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> *65* years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

BURINEX is contraindicated in patients who are hypersensitive to this drug, other sulfonamide derivatives or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

- Anuria
- Hepatic encephalopathy including coma
- Severe electrolyte depletion
- Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

BURINEX is a potent diuretic which, if given in excessive amounts, can lead to profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required and dose and dosage schedule have to be adjusted to the individual patient's needs (see Dosage and Administration).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Dosage should be individualized with careful monitoring of patient response
- In patients with hepatic failure the dosage should be kept to a minimum, and if necessary, dosage increased very carefully. A maintenance dose as low as 0.5 mg daily should be considered and the daily dose should not exceed 5 mg. (See Warnings and Precautions)

4.2 Recommended Dose and Dosage Adjustment

The usual total oral daily dosage of BURINEX is 0.5 to 2.0 mg and in most patients may be given as a single dose.

If the diuretic response to an initial 1 mg dose of BURINEX is not adequate, a second or third dose may be given at 4 to 5 hour intervals. The maximum recommended daily dose is 10 mg.

Health Canada has not authorized an indication for pediatric use (see 1.1 and 7.1.3).

4.3 Administration

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 edema.

4.4 Missed Dose

If a dose was missed, it should be taken as soon as the patient remembers. If the next dose is due in less than four hours that dose should be omitted and the next dose taken at the usual time. A dose should not be doubled to make up for a missed dose.

5 OVERDOSAGE

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

Profound water loss and electrolyte depletion, dehydration, reduction of blood volume and circulatory collapse with a possibility of vascular thrombosis and embolism.

Treatment
Discontinue the drug. Treatment is by water and/or electrolyte replacement.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 1 mg, 5 mg	Agar, Colloidal Anhydrous Silica, Lactose, Maize starch, Magnesium stearate, Microcrystalline cellulose, Polysorbate 80, Povidone,Talc

Tablets 1 mg: White, flat, circular (8 mm), uncoated, bevelled edge tablet, marked on one face with a score line and the number 133, and with an Assyrian Lion on the other face. Blister pack

of 30 tablets.

Tablets 5 mg: White, flat, circular (10 mm), uncoated bevelled edge tablet marked with a score line and “5 mg” on one face. Blister pack of 30 tablets.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

The dose of BURINEX should be adjusted to patient's need. Excessive doses or too frequent administration can lead to profound water loss, electrolyte depletion, dehydration, reduction in blood volume and circulatory collapse with a possibility of vascular thrombosis and embolism, particularly in elderly patients.

Patients under treatment should be observed regularly for possible occurrence of blood dyscrasias, liver damage, or idiosyncratic reactions which have been reported rarely in foreign marketing experience.

Driving and Operating Machinery

BURINEX 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.

Ear/Nose/Throat

The potential for ototoxicity with the use of BURINEX exists, particularly with at high treatment doses, or repeated use in patients with severe renal impairment. The ototoxic effects of aminoglycosides may be increased by concomitant administration of potent diuretics such as BURINEX. (see 9.2 Drug-Drug Interactions).

Endocrine and Metabolism

Hypokalemia can occur as a consequence of BURINEX administration. Prevention of hypokalemia requires particular attention in the following conditions: patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis and ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, certain diarrheal states, or other states where hypokalemia is thought to represent particular added risks to the patient, (i.e.) history of ventricular arrhythmias.

Since rigid sodium restriction is conducive to both hyponatremia and hypokalemia, such restriction is not advisable in patients on BURINEX therapy.

Administration of proton pump inhibitors has been associated with development of hypomagnesaemia. Hypomagnesaemia may be exacerbated with co-administration of BURINEX, therefore magnesium levels should be measured before and periodically when this combination is used.

Electrolyte disturbances can occur especially during long term treatment.

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

Gastrointestinal
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 (see, CONTRAINDICATIONS).

Hepatic/Biliary/Pancreatic
In patients with hepatic cirrhosis and ascites, sudden alterations of electrolyte balance may precipitate hepatic encephalopathy and coma.

Therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

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

Immune
If known hypersensitivity to sulphonamides there may be a potential risk of hypersensitivity to BURINEX (see, CONTRAINDCATIONS).

Monitoring and Laboratory Tests
Serum electrolyte determination should be performed frequently.

Serum potassium concentrations should be monitored regularly and potassium supplements or potassium sparing diuretics may be required especially when high doses are used for prolonged periods. Particular caution with potassium concentration is necessary in patients receiving digitalis glycosides or potassium depleting steroids. Periodic determination of other electrolytes is also advised, particularly in patients on low salt diets.

Electrolyte and fluid imbalance may occur and replacement therapy should be instituted where indicated to avoid any risk of electrolyte depletion, hypovolemia or hypotension.

Renal
BURINEX may increase urinary calcium excretion with resultant hypocalcemia.

Reversible elevation of BUN and creatinine may occur, especially in association with dehydration and in patients with renal insufficiency. Marked increases in BUN and creatinine or the development of oliguria during treatment of patients with progressive renal disease is an indication for discontinuation.

BURINEX may cause an increase in blood uric acid.

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

Dope Tests
BURINEX is banned for use in sports. Taking BURINEX will lead to disqualification for athletes. This drug can be detected in the urine during routine dope testing.

Sexual Health
Fertility
There are no clinical studies with BURINEX regarding fertility.

Vascular disorder
If you have hypotension, the dosage of BURINEX should be reduced or the drug stopped.

7.1 Special Populations

7.1.1 Pregnant Women

BURINEX 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 BURINEX. It may be used only in case of heart failure when the potential benefit justifies the potential risk to the foetus.

7.1.2 Breast-feeding

Since BURINEX passes into the breast milk, the drug should not be used during breast-feeding.

7.1.3 Pediatrics

Pediatrics (18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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), fatigue occurring in approximately 3% of patients and muscle cramps (>1%).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Drug Reactions Occurring in ≥ 1% of Patients

	BURINEX n = 369
Gastrointestinal disorders	Nausea, Abdominal pain
General disorders and administration site conditions	Oedema peripheral
Metabolism and nutrition disorders	Electrolyte imbalance (including hypokalaemia, hyponatraemia, hypochloraemia and hyperkalaemia
Musculoskeletal and connective tissue disorders	Muscle cramps
Nervous system disorders	Dizziness
Renal and urinary disorders	Micturition disorder
Respiratory, thoracic and mediastinal disorders	Dyspnoea

8.3 Less Common Clinical Trial Adverse Reactions

Ear and labyrinth disorders: Impaired hearing, ear discomfort

Gastrointestinal disorders: Abdominal pain, vomiting, diarrhoea, constipation, dry mouth, upset stomach

General disorders and administration site conditions: Chest pain, malaise/weakness, thirst, fatigue, sweating

Investigations: Electrocardiogram changes

Metabolism and nutrition disorders: Gout, dehydration

Musculoskeletal and connective tissue disorders: Arthralgia, musculoskeletal pain, muscle spasms

Nervous system disorders: Headache, encephalopathy (in patients with pre-existing liver disease), vertigo, asterixis

Renal system disorders: renal failure

Reproductive system and breast disorders: nipple tenderness, premature ejaculation and difficulty maintaining an erection

Respiratory, thoracic and mediastinal disorders: Cough, hyperventilation

Skin and subcutaneous tissue disorders: Pruritus, urticaria (hives), rash, sweating

Vascular disorders: Hypotension

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Laboratory abnormalities reported have included hyperuricemia (18.4%), hypochloremia (14.9%), hypokalemia (14.7%), azotemia (10.6%), hyponatremia (9.2%), increased serum creatinine (7.4%), hyperglycemia (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 BURINEX these conditions may become more pronounced by intensive therapy.

Diuresis induced by BURINEX may also rarely be accompanied by changes in LDH (1.0%), total serum bilirubin (0.8%), serum proteins (0.7%), SGOT (0.6%), SGPT (0.5%), alkaline phosphatase (0.4%), cholesterol (0.4%) and creatinine clearance (0.3%). Also reported have been thrombocytopenia (0.2%) deviations in hemoglobin (0.8%), prothrombin time (0.8%), hematocrit (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.

8.5 Clinical Trial Adverse Reactions (Pediatrics)

The safety profile of BURINEX has not been established in the pediatric population.

8.6 Post-Market Adverse Reactions

Blood and lymphatic system disorders: Bone marrow failure and pancytopenia, thrombocytopenia, leukopenia including neutropenia, anaemia

Cardiac disorders: Chest discomfort

Gastrointestinal disorders: Abdominal discomfort

Metabolism and nutrition disorders: Glucose metabolism disorder and hyperuriaemia

Musculoskeletal and connective tissue disorders: Myalgia

Nervous system disorders: Fatigue (including lethargy, somnolence, asthenia), syncope

Renal and urinary disorders: Renal impairment

Skin and subcutaneous tissue disorders: Rash (various types of rash reactions such as erythematous, maculo-papular and pustular have been reported), dermatitis and eczema, photosensitivity.

9 DRUG INTERACTIONS

9.1 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 1 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence*	Effect	Clinical comment
Digitalis glycosides	C	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	C	Hypokalaemia increases the sensitivity to non-depolarising neuromuscular blocking agents.	Use with caution.
Lithium	C	BURINEX reduces lithium clearance resulting in high serum levels of lithium.	Lithium should generally not be given with diuretics such as BURINEX. Concomitant therapy requires close monitoring of serum lithium levels. Lower lithium doses may be required.
Antiarrhythmics	C	Concomitant use of BURINEX 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.
Probenecid	T	Probenecid inhibits the renal tubular secretion of bumetanide leading to a diminished natriuresis.	Use with caution.
NSAIDs	C	BURINEX may enhance the nephrotoxicity of Non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs inhibit the effect of BURINEX.	The effects of concurrent use should be monitored (e.g. blood pressure, signs of renal failure).
Anti-hypertensive agents and medicinal products inducing postural hypotension	C	BURINEX may potentiate the effect of anti-hypertensive agents including diuretics and drugs inducing postural hypotension (e.g. tricyclic antidepressants).	First-dose hypotension may occur.

Potassium depleting agents	C	The potassium depleting effect of BURINEX may be increased by other potassium depleting agents.	Simultaneous administration should generally be avoided especially in patients with impaired renal function
Aminoglycosides	C	BURINEX may enhance the nephrotoxicity of aminoglycosides. The ototoxic effects of aminoglycosides may be increased by concomitant administration of potent diuretics such as BURINEX.	Use with caution.

*Case study (C), clinical trial (CT) or theoretical (T)

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

BURINEX is a loop diuretic. The diuretic effect of BURINEX results largely from the inhibition of sodium reabsorption in the ascending limb of the loop of Henle. This is shown by a marked reduction in freewater clearance during hydration and tubular solute-free water reabsorption during hydropenia.

10.2 Pharmacodynamics

BURINEX may have an additional action in the proximal tubule, since phosphaturia has been observed during BURINEX induced diuresis and the renal clearance of BURINEX is decreased by probenecid. The proximal tubular activity does not seem to be related to an inhibition of carbonic anhydrase. Potassium excretion is increased by BURINEX in a dose-related fashion.

Pharmacological and clinical studies have shown that 1 mg BURINEX produces a diuretic response similar to that of approximately 40 mg furosemide.

10.3 Pharmacokinetics

Animal
In the dog, bumetanide causes a marked increase in urine flow without significant alterations in urine osmolality. It enhances excretion of sodium, chloride and potassium at oral doses as low as 0.005 mg/kg. Sodium reabsorption is reduced from 98% in control periods to 79% during I.V. infusion. Maximum diuresis occurs at 1-2 hours after oral or I.V. administration and lasts 3-6 hours.

Bumetanide significantly reduces the clearance of para-aminohippuric acid (PAH) in dogs. Creatinine clearance is not significantly altered.

Human
After oral administration of 1 mg of BURINEX diuresis begins within 30 minutes with a peak effect between 1 and 2 hours. Diuresis is nearly completed after 3 to 4 hours.

Absorption: Following oral administration to normal subjects, BURINEX is rapidly and almost completely (>80%) absorbed from the gastrointestinal tract. The time to reach peak blood levels is 0.5-2 hours. Plasma protein binding of BURINEX is approximately 95%.

Elimination: BURINEX is rapidly eliminated, the plasma half-life being 1.5 hours. The majority (approx. 80%) of an oral dose of BURINEX is recovered in the urine (about 60% of this as unchanged bumetanide, the remainder as metabolites).

11 STORAGE, STABILITY AND DISPOSAL

1 mg tablet: Store below 30 °C
5 mg tablet: Store at 15-25 °C

To protect from light keep the blister in outer carton.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

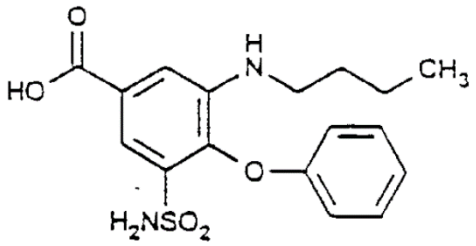
Drug Substance

Proper name: Bumetanide

Chemical name: 3-Butylamino-4-phenoxy-5-sulphamoyl-benzoic acid

Molecular formula and molecular mass: $C_{17}H_{20}N_2O_5S$, 364.41

Structural formula:



Physicochemical properties: White crystalline powder with a slightly bitter taste, sensitive to light. Slightly soluble in water, ether and chloroform, moderately soluble in 96% ethanol and acetone with a melting point of 233-234°C and approximate pka values 0.3-4-10.

13 CLINICAL TRIALS

13.1 Comparative Bioavailability Studies

BURINEX (2 X 0.5 mg Tablets vs. 1 X 1.0 mg Tablet) Geometric Mean Arithmetic Mean (CV %)			
	BURINEX 2 x 0.5 mg tablets	**BURINEX 1 x 1.0 mg tablet**	**% Ratio of Geometric Means**
AUC_T (G.M.) (µg.hr/L) (A.M.(CV))	76.17 79.31 31.0	74.21 76.75 26.6	102.6
AUC_I (G.M.) (µg.hr/L) (A.M.(CV))	86.31 89.33 28.7	85.10 87.25 22.9	101.4
C_{max} (G.M.) (µg/L) (A.M.(CV))	41.28 43.14 30.7	39.62 41.38 28.8	104.2
T_{max} (A.M.(CV)) (h)	1.00 46.2	1.14 41.4	-

BURINEX (2 X 0.5 mg Tablets vs. 1 X 1.0 mg Tablet) Geometric Mean Arithmetic Mean (CV %)			
$T_{1/2}$ (h) (A.M.(CV))	1.02 20.0	1.00 20.1	-

The T_{max} and $T_{1/2}$ parameters are expressed as the arithmetic means (CV%) only.

14 NON-CLINICAL TOXICOLOGY

14.1 Acute Toxicity

In rabbits, ataxia, lacrimation and tremors were observed. These symptoms were not observed in mice or rats.

Species	Route	LD (mg/kg) mean ± SD
Mice	P.O. I.P. S.C. I.V.	930 ± 49 280 ± 13 570 ± 33 > 150 **
Adult rats	P.O. I.P. I.V.	> 2000 310 ± 15 > 150 **
Neonatal rats	P.O.	480 ± 47
Rabbits	P.O. I.V.	800 ± 125 70 *

* 14 day observation period
** 2 day observation period

14.2 Chronic Toxicity

Rats: Bumetanide was administered orally at doses of 10, 30 and 60 mg/kg/day to 3 groups of 60 male and 60 female rats for 78 weeks. Convulsive episodes (not dose-related) were noted in some treated (30%) and one control rat; most convulsions occurred immediately after dosing.

A dose related increase in the incidence of renal dystrophic calcifications was noted. Ovarian weight was reduced in the mid and high dose groups and the incidence of testicular atrophy was increased in males in the high dose groups. The incidence of mammary tumors was slightly increased in females of the middle and high dose groups.

In order to clarify the tumorigenic potential of bumetanide, the 78 week rat toxicity study was repeated using the same doses in groups of 80 males and 80 females. The oral administration of bumetanide did not increase the prevalence of mammary tumors nor affect the profile of spontaneous tumors in the rat.

Dogs: Bumetanide was administered orally for 1 year to 3 groups of 3 male and 3 female dogs

at dose levels of 0.12, 0.4 and 1.2 mg/kg/day. Tubular atrophy and dilation associated with varying degrees of chronic inflammatory cell infiltration and fibrosis, atrophic glomeruli, capsular thickening and fluid filled capsular cysts occurred in the kidneys of high and mid-dose group dogs.

Baboons: Bumetanide was administered orally to 4 groups of 3 male and 3 female baboons for 26 weeks at dose levels of 0.1, 1.0, 5.0 and 10 mg/kg/day. After 4 weeks of dosing, the 5.0 and 10 mg/kg/day dose levels were reduced to 2.5 and 5.0 respectively because the animals appeared dehydrated. One high dose female was sacrificed because of marked deterioration in general condition.

Histological examination showed calcified material associated with macrophages and inflammatory cells with eosinophilic granular casts in the renal tubules of the two high dose groups.

14.3 Mutagenicity

Bumetanide was devoid of mutagenic activity in various strains of Salmonella typhimurium when tested in the presence of an in vitro metabolic activated system.

14.4 Reproductive Studies

Mice: Doses of 0.05, 0.25 and 0.50 mg/kg/day were administered orally to 3 groups of 15 pregnant Hauschka/Nirand mice from day 6 through day 16 of gestation. A slight increase in fetal deaths and resorptions was noted at the high dose. No malformations were observed.

Doses of 10, 30 and 100 mg/kg/day were administered to groups of 22 to 25 Charles River CD-1 mice from day 6 to day 15 of gestation. No signs of toxicity were observed.

Bumetanide is neither teratogenic nor embryotoxic in mice when given in doses up to 3400 times the maximum human therapeutic dose.

Rats: Doses of 10, 30 and 100 mg/kg/day were administered orally to 3 respective groups of 40 female rats from day 15 prior to mating. The same doses were administered to 3 respective groups of 20 male rats from day 84 prior to mating. Dose-related increases in fetal mortality were observed. No malformations were observed.

Similar doses were administered to 30, 26 and 27 pregnant females from day 6 to day 15 of gestation. No effect on fetal mortality was seen. Moderate growth retardation and an increased incidence of delayed ossification of sternebrae were observed in pups at 100 mg/kg/day. These effects were associated with maternal weight reduction during dosing. No such adverse effects were observed at 30 mg/kg/day. No malformations were observed.

Hamster: Bumetanide was not teratogenic in the hamster at an oral dose of 0.5 mg/kg/day.

Rabbits: Doses of 0.03, 0.10 and 0.30 mg/kg/day were administered orally to groups of 7 to 12 rabbits from day 6 to day 18 of gestation. Dams receiving the high dose showed depressed activity. A dose-related decrease in litter size and an increase in resorption rate were noted at oral doses of 0.1 and 0.3 mg/kg/day. A slightly increased incidence of delayed ossification of sternebrae occurred at 0.3 mg/kg/day; however, no effects were seen at 0.03 mg/kg/day.

The sensitivity of the rabbit to bumetanide parallels the marked pharmacologic and toxicologic effects of the drug in this species.

14.5 Other Studies

In studies with 49 cats, 55 dogs and guinea pigs, bumetanide was found to produce dose-related depressions of the auditory afferent action potentials (N1) and cochlear microphonics following intravenous administration.

In these test animals BURINEX was 5 to 6 times more potent than furosemide and, since the diuretic potency of BURINEX is about 40 to 60 times greater, it is anticipated that blood levels necessary to produce ototoxicity in humans will rarely be achieved.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrBURINEX®
Bumetanide Tablets

Read this carefully before you start taking **Burinex®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Burinex®**.

Serious Warnings and Precautions

Burinex® is a strong diuretic. Diuretics are also known as "water pills." Taking too much Burinex® can cause you to lose too much water and too many electrolytes. You must be supervised by a doctor while taking this drug. Your doctor will adjust your dose and your dosing schedule to treat your particular condition.

What is Burinex® used for?

Burinex® is used to treat the swelling in your body that is caused by excess fluid in your tissues (edema) that happens as a result of:

- congestive heart failure, or
- liver disease (cirrhosis), or
- kidney disease, including nephrotic syndrome

How does Burinex® work?

Edema means your body is retaining water. It can lead to swollen feet or ankles or trouble breathing. Burinex® works to remove the excess water by making your kidneys produce more urine.

What are the ingredients in Burinex®?

Medicinal ingredients: bumetanide

Non-medicinal ingredients: agar, colloidal anhydrous silica, lactose, magnesium stearate, maize starch, microcrystalline cellulose, polysorbate 80, povidone, talc.

Burinex® comes in the following dosage forms: 1 mg and 5 mg tablet.

Do not use Burinex® if you:

- are allergic to bumetanide or any of the other ingredients in this medicine or products containing sulfonamide
- cannot pass urine or the amount of urine you pass is very low
- are dehydrated or told you have very low blood levels of potassium, sodium or chloride.
- have severe liver disease or have a decline in brain function, including coma as a result of liver failure
- have problems digesting or absorbing galactose, lactose, or glucose-galactose

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Burinex®. Talk about any health conditions or problems you may have,

including if you:

- Have liver disease
- Have kidney disease
- Have low blood pressure
- Have abnormal levels of potassium in your blood
- Have gout
- Are taking a medicine (proton pump inhibitor) to treat acid reflux or peptic ulcers
- Have diabetes. Burinex® may affect your glucose (blood sugar) levels
- Are allergic to lactose (milk sugar) or milk protein. Lactose is an ingredient in Burinex®
- Are pregnant or planning on becoming pregnant
- Are breast-feeding

Other warnings you should know about:
Ear toxicity: Taking Burinex®, especially at high doses, may have a toxic effect on the ears. This may result in damage to the inner ears that are responsible for hearing and balance.

Liver Damage: Taking Burinex® may lead to abnormal changes in your blood cells or cause liver damage.

Effect on Blood Calcium Levels: Taking Burinex® may increase the amount of calcium passing into the urine. This can lead to low calcium levels in your blood.

Dope Tests: Burinex® is banned for use in sports. Taking Burinex® will lead to disqualification for athletes. This drug can be detected in the urine during routine dope testing.

Laboratory Tests: Your doctor should do regular blood tests to check your:

- potassium levels
- electrolyte levels

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Burinex®:

- Drugs used to treat heart conditions (such as digoxin) and drugs used to treat irregular heartbeats (such as antiarryhthmic drugs)
- Muscle relaxants given by injection before a general anaesthetic
- Lithium, a drug used to treat mood disorders. Do not take Lithium while taking Burinex®
- Non-steroidal anti-inflammatory drugs (NSAIDs) used to treat pain and swelling. You should avoid taking these drugs while taking Burinex®. Using Burinex® with NSAIDs can be harmful to your kidney's.
- Probenecid, a drug used to treat gout. You should avoid taking this drug while taking Burinex®
- Anti-hypertensive drugs used to treat high blood pressure
- Anti-depressants that can cause low blood pressure
- Drugs that affect the amount of potassium in your blood
- Aminoglycoside antibiotics (such as neomycin) which can affect hearing. You should avoid taking this drug while taking Burinex®. Using Burinex® with aminoglycoside antibiotics can be harmful to your kidney's.

How to take Burinex®:
It is recommended that you take Burinex® either:
- daily **or**
- on alternate days **or**
- for 3 to 4 days in a row and then wait 1 to 2 days before your next dose.

Usual Adult dose:
A usual dose of Burinex® may range from 0.5 to 2 mg per day. Your doctor will decide the best dose for you. Take it exactly as your doctor has told you. Your doctor will monitor you while you are taking Burinex®. Do not exceed 10 mg / per day.

Children under 18 years old should not use Burinex®.

Patients with liver failure: Use with caution. It may be necessary to adjust your dose. Follow your doctor's instructions.

Overdose:
Taking too much Burinex® can lead to:
- excessive water loss
- a lower amount of electrolytes. You may feel weak, dizzy, confused, tired, have cramps or vomiting if your electrolytes are low.
- dehydration
- low blood volume
- circulatory failure

You should **stop** taking Burinex® and restore the loss of water and electrolytes.

If you think you have taken too much Burinex®, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take a dose, take it as soon as you remember. If your next dose is due in less than 4 hours wait and take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

What are possible side effects from using Burinex®?
These are not all the possible side effects you may feel when taking Burinex®. If you experience any side effects not listed here, contact your healthcare professional.

Side effects include:
- muscle cramps
- dizziness
- low blood pressure
- headache
- nausea
- abnormal brain function in patients who have liver disease

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Increased production of urine: loss of water and electrolytes	**X**		
Low blood pressure: dizziness when standing up, lightheadedness		**X**	
Muscle problems: muscle pain, tenderness, weakness, cramps		**X**	
Decreased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally not feeling well			**X**
Electrolyte imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat			**X**
UNCOMMON			
Hearing problems: deafness, sometimes non-reversible		**X**	
Dehydration: dry mouth, increased thirst, feeling tired or sleepy, passing less urine, headache, dizziness			**X**
Increased blood sugar: frequent urination, thirst and hunger		**X**	
Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swelling or breathing			**X**
Kidney disease: more or less urine than usual, passing red urine or passing urine at night, difficulty or inability to pass urine			**X**

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
1 mg tablet: store below 30°C
5 mg tablet: store at 15-25 °C.
Keep the blisters in the carton to protect from light. Do not use after the expiry date (EXP).
Keep out of the reach and sight of children.

If you want more information about Burinex®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); or by contacting the sponsor, Karo Pharma AB, at medinfoca@karopharma.com, or by calling 1-800-780-6649.

This leaflet was prepared by Karo Pharma AB.

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