SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bumetanide Tablets 1mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1mg of bumetanide.

Excipient with known effect: Contains 50.6 mg of lactose monohydrate

For the full list of excipients,see section6.1.

3 PHARMACEUTICAL FORM

Tablet

White to off-white, round, normal convex, uncoated tablet of approximately 6 mm, plain on one side with a breakline and '1' centrally above 'BMT' on the other side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bumetanide Tablets 1mg are indicated in adults whenever diuretic therapy is required in the treatment of oedema, for example that associated with congestive heart failure, cirrhosis of the liver and renal disease including the nephrotic syndrome.

In oedema of cardiac or renal origin where high doses of a potent short acting diuretic are required, Bumetanide Tablets 5mg may be used in adults.

4.2 Posology and method of administration

Posology

The dose should be carefully titrated in each patient according to the patient's response and the required therapeutic activity.

Adults:

Most patients require a daily dose of 1mg which can be given as a single morning or early evening dose. Depending on the patient's response, a second dose can be given six to eight hours later. In refractory cases, the dose can be increased until a satisfactory diuretic response is obtained, or infusions of Bumetanide can be given.

The maximum daily dosage is 10mg.

Paediatric population:
The medicinal product is not recommended for children under 12 years of age as there is limited information on safety, efficacy and dosage in children.

Elderly:
Adjust dosage according to response; a dose of 0.5mg of bumetanide per day may be sufficient in some elderly patients.

Method of administration
For oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance, sulfonylureas or any of the excipients listed in section 6.1.
- Oliguria or anuria during treatment of severe progressing renal disease, (although Bumetanide can be used to induce diuresis in renal insufficiency)
- Comatose or precomatose states associated with liver cirrhosis
- Severe electrolyte depletion
- Renal failure associated with hepatic coma or caused by poisoning by hepatotoxic agents.

4.4 Special warnings and precautions for use

Excessively rapid mobilisation of oedema particularly in elderly patients, may give rise to sudden changes in cardiovascular pressure-flow relationships with circulatory collapse. This should be borne in mind when Bumetanide is given in high doses intravenously or orally.

Electrolyte disturbances may occur particularly in those patients taking a low-salt diet. Regular checks of serum electrolytes, in particular sodium, potassium, chloride and bicarbonate should be performed and replacement therapy instituted where indicated (see section 4.3).

Patients with chronic renal failure on high doses of Bumetanide should remain under constant hospital supervision. Bumetanide should be used with caution in patients already receiving nephrotoxic drugs. In these patents close monitoring of fluid status and renal function is required (see section 4.3, 4.5).

Increased risk of ototoxicity when bumetanide is used in renal impairment, excessive doses, and concurrent use of other ototoxic drugs (see section 4.5).

Bumetanide should be used with caution in patients with hypotension and those on antihypertensive drugs (see section 4.5).

As with other diuretics, bumetanide may cause an increase in blood uric acid. Asymptomatic hyperuricemia has been reported with use.

Periodic checks on urine and blood glucose should be made in diabetics and in patients suspected of latent diabetes (see section 4.5 and 4.8).

Encephalopathy may be precipitated in patients with pre-existing hepatic impairment (see section 4.3).

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.

Bumetanide Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Bumetanide Tablets contain less than 1 mmol sodium (23mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

In common with other diuretics, serum lithium levels may be increased when lithium is given concomitantly with bumetanide. This may result in increased lithium toxicity, including increased risk of cardiotoxic and neurotoxic effects of lithium. Therefore, it is recommended that lithium levels are carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination.

The toxic effects of nephrotoxic drugs may be increased by concomitant administration of potent diuretics such as bumetanide. Impairment of renal function may develop in patients receiving treatment with bumetanide and high doses of certain cephalosporins.

Bumetanide may potentiate the ototoxicity of aminoglycosides and other ototoxic drugs. Since this may lead to irreversible damage, these drugs must not be used with Bumetanide unless there are compelling medical reasons. In such situations, careful medical supervision is required.

Like other loop diuretics, bumetanide shows a tendency to increase the excretion of potassium causing hypokalaemia. There is increased risk of hypokalaemia when loop diuretics are given with acetazolamide, amphotericin, corticosteroids, thiazides and related diuretics, high doses of beta2 sympathomimetics, theophylline and reboxetine. Thus the dose may need adjustment when given in conjunction with these drugs.

Hypokalaemia caused by loop diuretics can lead to an increase in the sensitivity of the myocardium to the toxic effects of digitalis, amiodarone, disopyramide, flecainide, and increases the risk of ventricular arrhythmias with sotalol, amisulpride, sertindole, atomoxetine and pimozide.

Bumetanide may potentiate the effect of antihypertensive agents and drugs inducing postural hypotension such as tricyclic antidepressants.

Certain non-steroidal anti-inflammatory drugs have been shown to antagonise the action of diuretics and increase the risk of nephrotoxicity and increase the risk of hyperkalaemia.

Bumetanide may antagonise hypoglycaemic effect of antidiabetic drugs. Adjustment of the dose of antidiabetic drugs may be needed in concomitant use (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
For bumetanide no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal / foetal development, parturition or post natal development (see section 5.3).
The use of bumetanide in the first trimester of pregnancy should be avoided with caution exercised when prescribing to pregnant women in the remaining two trimesters.

Breast-feeding
Since it is not known whether bumetanide is distributed into breast milk, a nursing mother should either stop breast feeding or observe the infant for any adverse effects if the drug is absolutely necessary for the mother.

4.7 Effects on ability to drive and use of machinery

This medicine may have a small or moderate influence on the ability to drive or use machines. Bumetanide may cause fatigue and hypotension which may result in dizziness, light-headedness and blurred vision. Patients should not drive or use machines if they feel affected.

4.8 Undesirable effects

The following side effects, listed below by system organ class, have been reported to be associated with bumetanide or other loop diuretics. Since this information is mainly based on post marketing data, the frequency for these side effects is unknown.

Blood and lymphatic system disorders:
Thrombocytopenia, leukopenia, bone marrow depression, agranulocytosis,

Immune system disorders:
Hypersensitivity reactions

Metabolism and nutrition disorders:
Electrolyte imbalance, for example: Hypokalaemia, hyponatraemia, dehydration, hypomagnesaemia, gout, hyperuricaemia, alkalosis hypochloraemic, hyperglycaemia, hypocalcaemia, hyperlipidaemia.

Nervous system disorders:

Headache, dizziness, encephalopathy (in patients with pre-existing hepatic disease), paraesthesia

Ear and labyrinth disorders:
Tinnitus, hearing impairment, deafness, vertigo

Vascular disorders:
Orthostatic hypotension, hypotension

Gastrointestinal disorders:
Abdominal pain, nausea, vomiting, dyspepsia, diarrhoea, stomach cramps

Hepatobiliary system disorders:
Cholestasis, jaundice

Skin and subcutaneous tissue disorders:
Rash*, urticaria, dermatitis, photosensitivity reaction, pruritus
Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN).
*Various types of rash reactions such as erythematous, maculo-papular and pustular have been reported

Musculoskeletal, connective tissue and bone disorders:
Myalgia, muscle spasm, arthralgia

Renal and urinary disorders:
Renal failure acute

Reproductive system and breast disorders:
Gynaecomastia, breast pain

General disorders and administrative site conditions:
Fatigue, dehydration

Investigations:
Blood creatinine increased

High Dose Therapy
In patients with severe chronic renal failure given 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 up to 12 hours. The lowest reported dose causing this type of adverse reaction was 5 mg by intravenous injection and the highest was 75 mg orally in a single dose. All patients recovered fully and there was no deterioration in their renal function. The cause of this pain is uncertain but it 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.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
Symptoms would be those caused by excessive diuresis.

Management
Empty stomach by gastric lavage or emesis. General measures should be taken to restore blood volume, maintain blood pressure and correct electrolyte disturbance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diuretics, high-ceiling diuretics, sulfonamides, plain
ATC Code CO3 CA02

Mechanism of action
Bumetanide is a potent, high-ceiling loop diuretic with a rapid onset and a short duration of action.
The primary site of action is the ascending limb of the Loop of Henle where it exerts inhibiting effects on electrolyte reabsorption causing the diuretic and natriuretic action observed.

Clinical efficacy
After oral administration of a 1mg dose of Bumetanide, diuresis begins within 30 minutes with a peak effect between one and two hours. The diuretic effect is virtually complete in three hours after a 1mg dose.

5.2 Pharmacokinetic properties

Absorption
Bumetanide is well absorbed after oral administration with the bioavailability reaching between 80 and 95%.

Elimination
The elimination half-life ranges from between 0.75 to 2.6 hours.

Biotransformation
No active metabolites are known.

Renal or hepatic impairment
Renal excretion accounts for approximately half the clearance with hepatic excretion responsible for the other half. There is an increase in half-life and a reduced plasma clearance in the presence of renal or hepatic disease.

Chronic renal impairment
In patients with chronic renal failure the liver takes more importance as an excretory pathway although the duration of action is not markedly prolonged.

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 month 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 adminstration 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 was shown to be devoid of mutagenic activity in various strains of *Salmonella typhimurium* when tested in the presence or absence of an in vitro metabolic activation system.
An 18-month study showed an increase in mammary adenomas of questionable significance in female rats receiving oral doses of 60mg/kg/day (2000 times a 2mg human dose). A repeat study at the same doses failed to duplicate this finding. Reproduction studies were performed to evaluate general reproductive performance and fertility in rats at oral dose levels of 10, 30, 60 or 100 mg/kg/day. The pregnancy rate was slightly decreased in the treated animals; however, the differences were small and not statistically significant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose monohydrate
Magnesium stearate
Maize starch
Sodium lauryl sulfate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

AL/AL 39months
AL/PVC/PVdC 48 months

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

Bumetanide Tablets 1mg are packed in:
Aluminium/Aluminium or Aluminium/PVC/PVDC blisters in a carton box. The box may contain pack sizes of 20, 28, 30, 56, 60, 84 and 120 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Niche Generics Limited
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Hitchin
Hertfordshire
SG4 0TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 19611/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th July 1999
Date of latest renewal: 31st March 2005

10 DATE OF REVISION OF THE TEXT

26/11/2024