SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bumetanide 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of bumetanide.

Excipient with known effect:
Contains 265 mg lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, flat, bevelled-edged, scored, tablet marked “BU/5” on one side and “G” on the reverse, approx. diameter 10 mm.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4.1 Therapeutic indications

Bumetanide is indicated for the treatment of oedema associated with e.g. congestive heart failure, renal dysfunction including nephrotic syndrome and cirrhosis of the liver in adults.

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

4.2 Posology and method of administration

Posology

Adults: The dose should be carefully titrated in each patient according to the patient’s response and the required therapeutic activity. As a general rule, in patients not controlled on lower doses, dosage should be started at 5mg daily and then increased by 5mg increments every 12-24h until the required

response is obtained or until side effects appear. Consideration should be given to a twice daily rather than a once daily dosage.

Direct substitution of bumetanide for furosemide in a 1:40 ratio at high doses should be avoided. Treatment should be initiated at a lower equivalent dose and gradually increased at 5 mg increments.

Dosage in the elderly
Adjust the dosage according to the response. A dose of 0.5 mg bumetanide per day may be sufficient in some elderly patients.

Paediatric population
Not recommended for children under 12 years of age as there is limited information on safety, efficacy and dosage in children.

Method of administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance, sulfonamides or to any of the excipients listed in section 6.1.

Oliguria.
Anuria.
Increase in blood urea.

- Although bumetanide can be used to induce diuresis in renal insufficiency, any marked increase of blood urea or the development of oliguria or anuria during treatment of severe progressive renal disease are indications for stopping treatment with bumetanide.

Hepatic coma.
Severe electrolyte imbalance.
Concomitant administration with lithium salts (see section 4.5).

4.4 Special warnings and precautions for use

Sudden changes in cardiovascular pressure-flow relationships, leading to circulatory collapse, can occur particularly in the elderly if the oedema is eliminated too rapidly. It is important to remember this when bumetanide is given in high doses, either orally or intravenously.

Patients with chronic renal failure on high doses of bumetanide should remain under constant hospital supervision.

Patients on a low salt diet may suffer electrolyte imbalance. Serum electrolyte checks, in particular for sodium, potassium, chloride and bicarbonate, should be carried out on a regular basis and, where necessary, replacement therapy carried out.

Bumetanide may enhance the nephrotoxicity or ototoxicity of other drugs, particularly in patients with renal impairment.

Bumetanide may precipitate encephalopathy in patients with hepatic impairment.

Bumetanide may increase uric acid. Blood glucose and blood uric acid should be measured periodically, especially in diabetics and those suspected of latent diabetes and in patients with gout.

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations with bumetanide are considered potentially hazardous:

Bumetanide should not be administered concurrently with lithium, as diuretics reduce the clearance rate of lithium leading to increased blood-lithium levels with signs of overdose (see section 4.3).

When bumetanide is used to treat oedema in hypertensive patients the dose of antihypertensive drug may need to be adjusted as bumetanide may potentiate its effects.

The dose of bumetanide may need to be adjusted when given in conjunction with cardiac glycosides, such as digitalis, since the increased potassium excretion resulting from bumetanide administration can cause an increased sensitivity of the myocardium to the toxic effects of glycosides.

Certain NSAIDS are known to have antagonistic effects on the action of diuretics.

Bumetanide should not be given concurrently with certain antibiotics and antifungals, such as cephaloridine or amphotericin as it could lead to increased toxic effects from these antibiotics and antifungals.

4.6 Fertility, pregnancy and lactation

Pregnancy
Although tests in animals have shown no teratogenic effects, there are no data on its effect on pregnant humans. Therefore it is advisable to avoid taking this drug during the first trimester.

Breast-feeding
There are no data on breast-feeding and therefore nursing mothers should stop bumetanide treatment during breast-feeding unless the drug is essential. In such cases, the infant should be observed for any adverse effects.

4.7 Effects on ability to drive and use machines

Bumetanide has no known effect on the ability to drive or operate machinery.

4.8 Undesirable effects

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).

Adverse effects are listed by system organ class and frequency: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data):

Blood and lymphatic system disorders
Rare: Bone marrow depression associated with the use of bumetanide, but it has not been proven definitely to be attributed to the drug.

Not known: thrombocytopenia.

Metabolism and nutrition disorders
Common: dehydration.

Uncommon: fluid and electrolyte depletion.

Not known: hyperuricaemia, hyperglycaemia.

Nervous system disorders
Common: dizziness, headache.

Not known: encephalopathy (in patients with pre-existing hepatic disease).

Ear and labyrinth disorders
Uncommon: ear pain, vertigo.

Rare: Hearing disturbance after administration of bumetanide, which is reversible.

Vascular disorders
Common: hypotension.

Gastrointestinal disorders
Common: nausea.

Uncommon: diarrhoea.

Not known: stomach cramps, abdominal pain, vomiting, dyspepsia.

Skin and subcutaneous tissue disorders
Common: pruritis (in patients with liver disease).
Not Known: Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN).

Uncommon: urticaria.

Not known: rash.

Musculoskeletal and connective tissue disorders
Not known: muscle cramps, arthralgia.

Reproductive system and breast disorders
Uncommon: painful breasts.

Not known: gynaecomastia.

General disorders and administration site conditions
Common: fatigue.

Uncommon: chest discomfort.

Investigations
Not known: raised blood urea and serum creatinine, abnormalities of serum levels of hepatic enzymes

<u>Higher dose therapy:</u>

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 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

Signs and symptoms
If overdose has occurred or is suspected symptoms should be those caused by excessive diuresis.

Management
Steps should be taken to empty the stomach either by emesis or gastric lavage. General measures should be taken to restore blood volume, maintain blood pressure and correct electrolyte disturbances.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diuretics, high-ceiling diuretics, sulfonamides, plain, ATC code: C03CA02.

Mechanism of action
Bumetanide is a potent 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 its diuretic and natriuretic action.

Clinical efficacy
After oral administration, the diuretic effect is seen within 30 minutes with the peak effect seen between 1 and 2 hours. The diuretic effect is practically complete in 3 hours after a 1mg dose.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, bumetanide is rapidly and almost completely absorbed from the gastro-intestinal tract with the bioavailability reported as between 80 and 95%.

Distribution
It is 95% bound to plasma proteins. It has a plasma elimination half-life of 0.75 to 2.6 hours.

Highest concentrations of the drug are achieved in the plasma, kidney and liver. It is not yet clear whether the drug crosses the placenta or passes into the cerebrospinal fluid.

Biotransformation and elimination
Bumetanide is cleared from the circulation at a rate of 120-250 ml/min with approximately half of an oral dose excreted unchanged via the kidneys with the remainder excreted via the bile into the faeces.

No active metabolites are known. The primary urinary metabolite is the 3' alcohol of the N-butyl chain and the primary biliary metabolite is the 2' alcohol.

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.

Renal and hepatic impairment
There is an increase in half-life and a reduced plasma clearance in the presence of renal or hepatic impairment.

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.

5.3. Preclinical Safety Data

Bumetanide has been extensively evaluated in a wide range of animal toxicity tests. Studies in rats and mice have shown it to have a relatively low acute

toxicity. No toxic effects were seen in rats at doses of up to 50 mg/kg/day over a 26 week period. In thirteen and 26 week studies at doses of up to 100 mg/kg/day, haematological and clinical chemistry values were generally unaffected; other effects seen were generally related to the diuretic effects of the drug.

Reproductive studies have shown no teratogenic or embryotoxic effects at oral doses up to 50 mg/kg/day in rats and 100 mg/kg/day in mice. But at 3400 times the standard human dose embryocidal effects (growth retardation and decreased foetal weight) were observed in rats. Although no foetal abnormalities occurred foetal toxicity was greater in rabbits: increased resorption rate was observed at doses of 0.25 and 0.5 mg/kg/day.

Bumetanide showed no evidence of mutagenicity on Ames testing. Seventy-eight week studies in rats do not suggest that bumetanide has a significant carcinogenic potential although damage to kidneys, testes and the auditory system were observed in post mortem examinations. In common with other 'loop' diuretics, diuretics, intravenous bumetanide caused ototoxicity in cats.

Overall, these studies provide satisfactory evidence for the likely safety of bumetanide when administered to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Maize starch, pregelatinised
Cellulose, microcrystalline
Magnesium stearate

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVdC/Al calendar blister packs: 5, 7, 10, 14, 15, 20, 21, 25, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 168 and 180 tablets.

High density polyethylene containers with tamper-evident polypropylene caps: 5, 7, 10, 14, 15, 20, 21, 25, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 168 and 180 tablets.

Polypropylene containers with tamper-evident polyethylene caps with optional polyethylene ullage filler: 5, 7, 10, 14, 15, 20, 21, 25, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 168 and 180 tablets.

Not all pack types/sizes may be marketed.

6.6. Instruction for Use/Handling

None.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd t/a Mylan
Station Close
Potters Bar
Herts
EN6 1TL

8. Marketing Authorisation Number

PL 04569/0434

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/08/2006

10 DATE OF REVISION OF THE TEXT

21/11/2024