

Public Assessment Report

Scientific discussion

**Furosemide 20 mg and 40 mg tabletten,
tablets
(furosemide)**

NL/H/4837/001-002/

Date: 1 March 2023

This module reflects the scientific discussion for the approval of Furosemide 20 mg and 40 mg tabletten, tablets. The procedure was finalised in the United Kingdom (UK/H/0754/001-002/). After a transfer in 2019, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Furosemide 20 mg Tablets BP Furosemide 40 mg Tablets BP

PL 17907/0203-4

UKPAR

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Furosemide 20 mg and 40 mg Tablets BP

PL 17907/0203-4

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal products Furosemide 20 mg and 40 mg Tablets BP (PL 17907/0203-4) on 15th November 2011. These are prescription-only medicines (POM).

Furosemide Tablets belong to a group of medicines called diuretics, which increase the amount of urine passed by the kidneys, helping to remove excess fluids from the body. Diuretics are also known as 'water tablets'.

Furosemide Tablets are used in the treatment of oedema (fluid retention) caused by disorders of the heart, kidneys or liver. The tablets may also be used to treat pulmonary oedema (build up of fluid in the lungs) and mild to moderate hypertension (high blood pressure).

These Marketing Authorisations for Furosemide 20 mg and 40 mg Tablets BP are considered to be identical to the previously granted licences for Furosemide 20 mg and 40 mg Tablets BP (PL 17907/0018-9), authorised to Bristol Laboratories Limited on 4th June 2003.

No new or unexpected safety concerns arose from these simple applications. It was judged that the benefits of Furosemide 20 mg and 40 mg Tablets BP outweigh the risk; hence Marketing Authorisations have been granted.

Furosemide 20 mg and 40 mg Tablets BP
PL 17907/0203-4

SCIENTIFIC DISCUSSION

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Very common: > 1/10	Common: > 1/100, < 1/10
Uncommon: > 1/1000, < 1/100	Rare: > 1/10000, < 1/1000
Very rare: < 1/10000, including isolated reports	

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Bristol Laboratories Limited Marketing Authorisations for the medicinal products Furosemide 20 mg and 40 mg Tablets BP (PL 17907/0203-4) on 15th November 2011. The products are prescription-only medicines.

These are simple, abridged, 'informed consent' applications, submitted according to Article 10(c) of EC Directive 2001/83 (as amended), cross-referencing the Marketing Authorisations for Furosemide 20 mg and 40 mg Tablets BP (PL 17907/0018-9), authorised to Bristol Laboratories Limited on 4th June 2003.

Furosemide Tablets are indicated for the following:

- The treatment of oedema associated with cardiac disease, liver disease, renal disease including nephrotic syndrome (in case of treatment failure with or intolerance to corticosteroids and in patients with nephrotic syndrome, therapy of the underlying disorder has priority) and pulmonary oedema.
- The treatment of mild to moderate hypertension (alone, or in combination with other antihypertensive agents in the treatment of more severe cases).

Furosemide is a potent, short and rapid-acting loop diuretic, belonging to the pharmacotherapeutic group of plain sulphonamides (ATC code: CO3C A01).

It inhibits the re-absorption of $\text{Na}^+ / 2\text{Cl}^- / \text{K}^+$ in the ascending part of Henle's loop by blocking the ion carrier for these ions. The fractional sodium excretion can amount to 35% of the total sodium in the glomerular filtrate. Increased sodium excretion leads secondarily to increased urinary excretion and to increased distal-tubular K^+ -secretion attributable to osmotically bound water. The excretion of Ca^{2+} and Mg^{2+} ions is also increased. Besides the losses of the above-mentioned electrolytes, excretion of uric acid may be reduced, and a shift of the acid-base balance towards metabolic alkalosis may occur.

Furosemide interrupts the tubuloglomerular feedback mechanism at the macula densa, so that the saluretic efficacy is not attenuated.

Furosemide leads to dose-dependent stimulation of the renin-angiotensin-aldosterone system. In case of cardiac insufficiency, furosemide leads to an acute reduction of the cardiac preload through dilatation of the venous capacitance vessels. This early vascular effect seems to be mediated through prostaglandins and requires sufficient renal function with activation of the renin-angiotensin-aldosterone system as well as intact prostaglandin synthesis.

Furosemide has an antihypertensive effect as a consequence of increased excretion of sodium chloride and reduced responsiveness of vascular smooth muscle cells to vasoconstrictive stimuli, and a reduction in blood volume.

The MHRA considers that the pharmacovigilance system described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

As the applications are for products that are identical to already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

It is not considered that these medicinal products represent any risk to the environment. There is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. The availability of these medicinal products, which are identical to the cited reference products, will not lead to any increase in environmental exposure concentrations of the active ingredient. An Environmental Risk Assessment (ERA) is not considered necessary.

No new data were submitted nor was it necessary for these simple applications, as the data are identical to those of the previously granted cross-reference products. As the cross-reference products were first granted prior to the introduction of current legislation, no Public Assessment Report (PAR) was generated for them.

PHARMACEUTICAL ASSESSMENT

LICENCE NUMBERS: PL 17907/0203-4

PROPRIETARY NAME: Furosemide 20 mg and 40 mg Tablets BP

ACTIVE INGREDIENTS: Furosemide

COMPANY NAME: Bristol Laboratories Limited

E.C. ARTICLE: Article 10(c) of Directive 2001/83/EC (as amended)

LEGAL STATUS: POM

1. INTRODUCTION

These are simple abridged applications, submitted under Article 10(c) of Directive 2001/83/EC (as amended) for Furosemide 20 mg and 40 mg Tablets BP. The proposed MAH is Bristol Laboratories Limited.

The reference products are Furosemide 20 mg and 40 mg Tablets BP (PL 17907/0018-9), authorised to Bristol Laboratories Limited on 4th June 2003. The proposed and reference products are identical.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The approved names of the products are Furosemide 20 mg and 40 mg Tablets BP. The products have been named in line with current requirements and the product names are acceptable.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

Each tablet contains 20 mg or 40 mg of the active ingredient furosemide. The tablets are licensed for marketing in the following packaging:

- polyvinylidene chloride (PVdC)/polyvinyl chloride (PVC) / aluminium foil blister strips - pack sizes of 28, 30, 50, 56, 84, 98 or 100 tablets
- High Density Polyethylene (HDPE) tablet containers - pack sizes of 100, 250, 500 and 1000 tablets

The blister strips and HDPE containers are packed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The MAH has stated that not all pack sizes may be marketed. The container closure systems and pack sizes are identical to those for the reference products.

The approved shelf-life (3 years) and storage conditions ('Do not store above 25°C. Store in the original package' for the blister packs; 'Do not store above 25°C. Keep the container tightly closed' for the HDPE container packs) are identical to the details registered for the reference products.

2.3 Legal status

POM - The products are available subject to a medical prescription.

2.4 Marketing Authorisation Holder / Contact Persons/Company

The proposed Marketing Authorisation Holder is 'Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts HP4 1EG'.

The Qualified Person (QP) responsible for pharmacovigilance was stated and their CV included.

2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the crossreference products and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition

The proposed compositions are consistent with the details registered for the crossreference products.

2.7 Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch sizes are stated.

2.8 Finished product / shelf-life specification

The proposed finished product specifications are in line with the details registered for the cross-reference products.

2.9 Drug substance specification

The proposed drug substance specifications are consistent with the details registered for the cross-reference products.

2.10 TSE Compliance

The magnesium stearate has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

3. EXPERT REPORT

A satisfactory quality overall summary has been prepared by an appropriately qualified expert. The CV of the expert was provided.

4. PRODUCT NAME & APPEARANCE

See 2.1 for details of the proposed product names. The 20 mg strength tablets are round, white to off-white tablets embossed 'F 20' on one side and 'BL' on the other side. The 40 mg strength tablets are round, white to off-white tablets embossed 'F 40' on one side and 'BL' on the other side. The 40 mg strength tablets have a scoreline, which is only to facilitate breaking for ease of swallowing and not to divide into equal doses. The appearances of the products are consistent with those of the crossreference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS

The approved SmPCs are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET (PIL) / LABELLING

PIL

The approved PIL is satisfactory and in line with the approved SmPCs. It has been prepared according to the Quality Review of Documents (QRD) template and is consistent with the details registered for the cross-reference products.

PIL user-testing has been accepted based on bridging to the successful user-testing of the PIL for the reference products, Furosemide 20 mg and 40 mg Tablets BP (PL 17907/0018-9). The text, content and layout of the proposed PIL are essentially identical to the approved PIL for the reference products. The bridging is accepted.

Labelling

Mock-ups of the labelling have been provided and are satisfactory. The approved artwork is comparable to the artwork registered for the cross-reference products and complies with statutory requirements.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for currently unmarketed pack sizes to the MHRA for approval before those packs are commercially marketed.

7. CONCLUSIONS

The grounds for these applications are considered adequate. Marketing Authorisations were therefore granted.

NON-CLINICAL ASSESSMENT

These are simple, abridged, 'informed consent' applications made under Article 10(c) of EC Directive 2001/83 (as amended).

No new non-clinical data have been supplied with these applications and none are required for applications of this type. A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the non-clinical expert has been supplied.

CLINICAL ASSESSMENT

These are simple, abridged, 'informed consent' applications made under Article 10(c) of EC Directive 2001/83 (as amended), cross-referring to the Marketing Authorisations for Furosemide 20 mg and 40 mg Tablets BP (PL 17907/0018-9; Bristol Laboratories Limited).

No new clinical data have been supplied with the applications, and none are required for applications of this type. A clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the clinical expert has been supplied.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The data for these applications are consistent with those previously assessed for the cross-reference products and as such have been judged to be satisfactory.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

These applications are considered identical to the previously granted licences for Furosemide 20 mg and 40 mg Tablets BP (PL 17907/0018-9; Bristol Laboratories Limited).

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The approved SmPCs, PIL and labelling are satisfactory and consistent with the details registered for the cross-reference products.

PIL user-testing has been accepted based on bridging to the successful user-testing of the PIL for the reference products, Furosemide 20 mg and 40 mg Tablets BP (PL 17907/0018-9).

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the MHRA for approval before those packs are marketed.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant's products are identical to the crossreference products. The benefit: risk ratio is considered to be positive.

Furosemide 20 mg and 40 mg Tablets BP PL 17907/0203-4

STEPS TAKEN FOR ASSESMENT

- 1 The MHRA received the marketing authorisation applications on 23rd May 2006.
- 2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 13th July 2006.
- 3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 9th January 2007, 12th January 2009 and 12th March 2009.
- 4 The applicant responded to the MHRA's requests, providing further information for the quality sections on 17th October 2008, 29th January 2009 and 11th May 2009 respectively.
- 5 The applications were determined on 15th November 2011.

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STEPS TAKEN AFTER AUTHORISATION

Not applicable

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Furosemide 20 mg and 40 mg Tablets BP (PL 17907/0203-4) is as follows – Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Furosemide 20 mg Tablets BP Furosemide 40 mg Tablets BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20/40 mg Furosemide Excipient(s): Each tablet contains 52.5/105 mg lactose monohydrate For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

40 mg: Round, white to off-white tablet embossed 'F 40' on one side and 'BL' on the other side.

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

20 mg: Round, white to off-white tablet embossed 'F 20' on one side and 'BL' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- 1) The treatment of oedema associated with cardiac disease, liver disease, renal disease including nephrotic syndrome (in case of treatment failure with or intolerance to corticosteroids and in patients with nephrotic syndrome, therapy of the underlying disorder has priority) and pulmonary oedema.
- 2) The treatment of mild to moderate hypertension (alone, or in combination with other antihypertensive agents in the treatment of more severe cases).

4.2 Posology and method of administration

For oral administration.

It is recommended that Furosemide tablets are taken on an empty stomach, and with plenty of liquid.

The usual initial adult dose is 20-40 mg daily, however the dose may need adjusting on an individual basis until an effective dose is achieved.

Hypertension: In mild to moderate hypertension the usual dose is 40 mg furosemide once daily.

In severe cases up to 60 mg furosemide per day. In case of insufficient response combination with non-diuretic anti-hypertensives is recommended.

Oedema associated with cardiac or hepatic diseases

The usual initial dose in adults is 20-40 mg furosemide. If the diuretic response is not satisfactory, the single dose can be doubled to 80 mg furosemide after 6 hours. If there is still inadequate diuresis, an additional dose of 160 mg furosemide can be given after a further 6 hours.

The daily maintenance dose is usually 40 - 80 mg furosemide.

Oedema associated with renal diseases

The usual initial dose in adults is 40 mg furosemide. If the diuretic response is not satisfactory, the single dose can be doubled to 80 mg furosemide after 6 hours. If there is still inadequate diuresis, an additional dose of 160 mg furosemide can be given after a further 6 hours.

The daily maintenance dose is usually 40 - 80 mg furosemide.

A higher dose (IV administration) may be required in patients with renal insufficiency.

In patients with nephrotic syndrome, the dosage must be determined with caution, because of the risk of a higher incidence of adverse reactions.

Children: The usual initial dose for oral furosemide in infants and children is 2mg/kg body weight given as a single dose. If the diuretic response is not satisfactory after the initial dose, dosage may be increased by 1 or 2 mg/kg no sooner than 6 to 8 hours after the previous dose (maximum of 40 mg daily).

Elderly: The dosage recommendations for adults apply. In general furosemide is eliminated more slowly in elderly patients; the dose should be titrated until a satisfactory response is achieved.

In case of renal insufficiency less furosemide will reach the renal tubules.

An increase of dose may be necessary to obtain the same diuretic effect.

No dosage adjustment is needed for patients with mild hepatic impairment; however the dosage may require adjustment in cases of moderate to severe hepatic impairment.

4.3 Contraindications

- Hypersensitivity to furosemide or any of the excipients of this product.
- Hypersensitivity to sulphonamides or sulphonamide derivatives (because of crosssensitivity between sulphonamides and furosemide).
- Hypovolaemia or dehydration (with or without accompanying hypotension).
- Anuria, or renal failure with anuria not responding to furosemide.
- Renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents or renal failure associated with hepatic coma.
- Pre-comatose and comatose states associated with hepatic encephalopathy.
- Severe hypokalaemia, severe hyponatraemia.
- Breast feeding.

4.4 Special warnings and precautions for use

Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition have an increased risk of developing acute retention and require careful monitoring.

Where indicated, steps should be taken to correct hypotension or hypovolaemia before commencing therapy.

Particularly careful monitoring is necessary in:

- patients with hypotension.
- patients who are at risk from a pronounced fall in blood pressure.
- patients where latent diabetes may become manifest or the insulin requirements of diabetic patients may increase.
- patients with gout. Serum uric acid levels tend to rise during treatment with Furosemide and an acute attack of gout may occasionally be precipitated.
- patients with hepatorenal syndrome.
- patients with hypoproteinaemia, e.g. associated with nephritic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated). Cautious dose titration is required.
- premature infants (possible development of nephrocalcinosis nephrolithiasis; renal function must be monitored and renal ultrasonography performed). In premature infants with respiratory distress syndrome, diuretic treatment with furosemide during the first weeks of life can increase the risk of persistent ductus arteriosus Botalli.

Cases of hypotension and hypovolemia need to be corrected before therapy is begun.

Serum cholesterol and triglyceride levels may rise during Furosemide treatment but will usually return to normal within six months.

Caution should be observed in patients liable to electrolyte deficiency. Regular monitoring of serum sodium, potassium, calcium, bicarbonate, urea uric acid, blood glucose level and creatinine is generally recommended during furosemide therapy; particularly close monitoring is required in patients at high risk of developing electrolyte imbalances or in case of significant additional fluid loss. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of furosemide.

During long term treatment with furosemide, a potassium rich diet is always indicated (e.g. potatoes, bananas, tomatoes, spinach, dry fruits). Sometimes a medicinal substitution of potassium is recommended. In other cases (i.e. liver cirrhosis), it is indicated to prevent hypokalaemia and metabolic alkalosis by administering a potassium sparing agent.

In case of renal insufficiency less furosemide will reach the renal tubules. An increase of dose may be necessary to obtain the same diuretic effect.

This medicinal product contains lactose. Patients with rare hereditary problems of fructose or galactose intolerance, the LAPP lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine, as it contains lactose.

The duration of administration depends on the nature and the severity of the disease.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on furosemide

Certain non-steroidal anti-inflammatory agents (e.g. indometacin, acetylsalicylic acid) may attenuate the action of furosemide and may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration.

Effect of furosemide on other medicinal products

Cardiac glycosides

In concurrent treatment with cardiac glycosides, it should be taken into account that if hypokalaemia and/or hypomagnesaemia develop during therapy with furosemide, the sensitivity of the myocardium towards cardiac glycosides is increased. There is an increased risk of ventricular arrhythmias (including torsades de pointes) when medicinal products that may cause prolongation of the QT interval (e.g. terfenadine, some antiarrhythmics of classes I and III) are used concomitantly, and in the presence of electrolyte imbalance.

Anti-hypertensive agents:

The dosage of concurrently administered antihypertensive agents may require adjustment.

ACE inhibitors:

The effects of other antihypertensives can be potentiated by concomitant administration of furosemide. Severe fall in blood pressure with shock in extreme cases and deterioration of renal function (acute renal failure in isolated cases) have been observed in combination with ACE inhibitors, when the ACE inhibitor was administered for the first time, or for the first time at high dosage (first dose hypotension). If possible, furosemide therapy should be temporarily discontinued (or at least the dose reduced) for three days before therapy with an ACE inhibitor is initiated or the dose of an ACE inhibitor is increased.

Nephrotoxic antibiotics:

The toxic effects of nephrotoxic antibiotics (e.g. aminoglycosides, cephalosporins, polymyxins) may be increased by concomitant administration of potent diuretics such as furosemide.

Ototoxic antibiotics:

Furosemide may potentiate the ototoxicity of aminoglycosides (e.g. kanamycin, gentamicin, tobramycin) and other ototoxic medicinal products. Since this may lead to irreversible damage, these medicinal products must only be used with furosemide if there are compelling medical reasons.

Non-steroidal anti-inflammatory agents:

Patients receiving high doses of salicylates concomitantly with furosemide, as in rheumatic disease, may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Lithium

In common with other diuretics, serum lithium levels may be increased when lithium is given concomitantly with furosemide, resulting in increased lithium toxicity. Therefore, it is recommended that lithium levels are carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination.

Others:

Oral furosemide and sucralfate must not be taken within 2 hours of each other because sucralfate decreases the absorption of furosemide from the intestine and so reduced its effect.

Furosemide may sometimes attenuate the effects of other products (e.g. the effects of antidiabetics and of pressor amines) and sometimes potentiate them (e.g. the effects of salicylates, theophylline, and curare-type muscle relaxants).

There is a risk of ototoxic effects if cisplatin and furosemide are given concomitantly. In addition, nephrotoxicity of cisplatin may be enhanced if furosemide is not given in low doses (e.g. 40 mg in patients with normal renal function) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

Attenuation of the effect of furosemide may occur following concurrent administration of phenytoin.

Concomitant administration of carbamazepine or aminoglutethimide may increase the risk of hyponatraemia.

Corticosteroids administered concurrently may cause sodium retention.

Corticosteroids, carbenoxolone, liquorice, B₂ sympathomimetics in large amounts, prolonged use of laxatives, reboksetine and amphotericin may increase the risk of developing hypokalaemia.

Probenecid, methotrexate and other products which, like furosemide, undergo significant renal tubular secretion may reduce the effect of furosemide.

Conversely, furosemide may decrease renal elimination of these products. In case of high-dose treatment (in particular, of both furosemide and the other medicinal products), this may lead to increased serum levels and an increased risk of adverse effects due to furosemide or the concomitant medication.

4.6 Fertility, Pregnancy and lactation

The teratogenic and embryotoxic potential of Furosemide in humans is unknown. Furosemide should not be used during pregnancy unless it is clearly necessary (for example such as in the case of maternal congestive heart failure) and the benefits to the mother outweigh the possible risk to the foetus.

Furosemide crosses placental barrier and can therefore cause increased diuresis of the foetus.

Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

In pregnancy furosemide should only be used on advice of a physician and should only be used if the oedema is not related to the pregnancy. Treatment of oedema and hypertension caused by pregnancy with diuretics is not advisable in general as the physiological hypovolaemia may be enhanced and the placental perfusion may be lowered. Treatment during pregnancy requires monitoring of foetal growth.

If use of furosemide is essential for the treatment of cardiac or renal insufficiency during pregnancy, careful monitoring of electrolytes, haematocrit and foetal growth is essential. Possible displacement of bilirubin from the albumin binding and thus elevated risk of nuclear icterus in hyperbilirubinaemia is discussed for furosemide.

Furosemide passes the placenta and reaches 100% of the maternal serum concentration in cord blood. No malformations in humans which might be associated with exposure to furosemide have been reported to date. However, there is insufficient experience to allow a concluding evaluation of a potential damaging effect in the embryo/foetus. *In utero* urinary production can be stimulated in the foetus. Urolithiasis has been observed after treatment of premature infants with furosemide.

Furosemide passes into breast milk and may inhibit lactation. Women must not breast feed if they are treated with Furosemide. If necessary, breastfeeding should be discontinued (see also section 4.3 "Contraindications").

4.7 Effects on ability to drive and use machines

Furosemide has minor or moderate influence on the ability to drive and use machines. It may reduce mental alertness.

4.8 Undesirable effects

The evaluation of adverse reactions is based on the following definition of frequency:

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SCIENTIFIC DISCUSSION

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Blood and lymphatic system disorders

Uncommon: thrombocytopenia Rare: eosinophilia, leukopenia Very rare: haemolytic anaemia, aplastic anaemia, agranulocytosis

Immune system disorders

Uncommon: pruritus, dermal and mucosal reactions (see skin and subcutaneous tissue disorders) Rare: fever, inflammation of blood vessels (vasculitis), renal inflammation (interstitial nephritis), severe anaphylactic and anaphylactoid reactions such as anaphylactic shock (for treatment see section 4.9 "Overdose")

Endocrine disorders

Glucose tolerance may decrease during treatment with furosemide, and hyperglycaemia may occur. This may lead to a deterioration of the metabolic status in patients with manifest diabetes mellitus. Latent diabetes mellitus may become manifest.

Metabolism and nutrition disorders

Impairment of electrolyte and fluid balance as a consequence of increased electrolyte excretion are commonly observed during therapy with furosemide. Regular monitoring of serum electrolytes (especially potassium, sodium and calcium) is therefore indicated.

Possible development of electrolyte disorders is influenced by underlying disorders (e.g. hepatocirrhosis, heart failure), concomitant medication (see section 4.5 "Interaction with other medicinal products and other forms of interaction") and nutrition.

As a result of increased renal sodium losses, hyponatraemia with corresponding symptoms may occur, particularly if the supply of sodium chloride is restricted. Commonly observed symptoms of sodium deficiency are apathy, systemma, inappetence, asthenia, somnolence, vomiting and confusion.

Particularly when the supply of potassium is concomitantly reduced and/or extrarenal potassium losses are increased (e.g. in vomiting or chronic diarrhoea), hypokalaemia may occur as a result of increased renal potassium losses. This is manifested as neuromuscular (myasthenia, paraesthesia, pareses), intestinal (vomiting, constipation, meteorism), renal (polyuria, polydipsia) and cardiac (impaired paced setting and conduction disorders) symptoms. Severe potassium losses may lead to paralytic ileus or disturbed consciousness, with coma in extreme cases.

Increased renal calcium losses can lead to hypocalcaemia, which may induce tetania in rare cases.

In patients with increased renal magnesium losses, tetania or cardiac arrhythmia were observed in rare cases as a consequence of hypomagnesaemia.

Metabolic alkalosis may develop, or existing metabolic alkalosis may be exacerbated, as a result of electrolyte and fluid losses during treatment with furosemide.

Hyperuricaemia occurs commonly during furosemide therapy. This may lead to acute episodes of gout in predisposed patients.

Serum levels of cholesterol and triglycerides may be elevated during furosemide treatment.

Nervous system disorders

Rare: paraesthesia

Ear and labyrinth disorders

Rare: On account of the ototoxic effects of furosemide, dysacusis and/or syrigmus (tinnitus aurium) can occur, but this is reversible in the majority of cases. This undesirable effect is particularly associated with too rapid i.v. injection, predominantly in patients with coexisting renal insufficiency or hypoproteinaemia (e.g. in nephrotic syndrome).

Cardiac disorders

In excessive diuresis, circulatory complaints may occur, particularly in elderly patients and in children. These are predominantly manifested as headache, vertigo, dysopia, xerostomia and thirst, hypotension and orthostatic dysregulation. Dehydration and - as a consequence of hypovolaemia - circulatory collapse and haemoconcentration may occur as a result of excessive diuresis. As a result of haemoconcentration, there may be an increased risk of thromboses, particularly in elderly patients.

Gastrointestinal disorders

Rare: gastrointestinal complaints (e.g. nausea, vomiting, diarrhoea)

Hepato-biliary disorders

Very rare: acute pancreatitis, intrahepatic cholestasis, increase in hepatic transaminases

Skin and subcutaneous tissue disorders

Uncommon: pruritus, dermal and mucosal reactions (e.g. bullous exanthema, urticaria, purpura, erythema multiforme, exfoliative dermatitis, photosensitivity) Rare: vasculitis

4.9 Overdose

The clinical picture in acute or chronic overdose depends primarily on the extent and consequences of electrolyte and fluid loss, e.g. hypovolaemia, dehydration, haemoconcentration, cardiac arrhythmias due to excessive diuresis. Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

Treatment should therefore be aimed at fluid replacement and correction of the electrolyte imbalance. Together with the prevention and treatment of serious complications resulting from such disturbances and of other effects on the body, this corrective action may necessitate general and specific intensive medical monitoring and therapeutic measures.

No specific antidote to furosemide is known. If ingestion has only just taken place, attempts may be made to limit further systemic absorption of the active ingredient by measures such as gastric lavage or those designated to reduce absorption (e.g. activated charcoal).

Emergency measures in case of anaphylactic shock

At the first signs (e.g. cutaneous reactions such as urticaria or flush, restlessness, headache, sudden, excessive perspiration, nausea, cyanosis):

- create a venous access
- in addition to other common emergency measures, head-chest down position, ensure airways are clear, administration of oxygen!
- if necessary, initiate further - possibly also intensive care - measures (among others administration of epinephrine, volume replacement, glucocorticoids).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: - Sulphonamide plain ATC code: CO3C A01

Furosemide is a potent, short and rapid-acting loop diuretic -.

It inhibits the re-absorption of $\text{Na}^+ / 2\text{Cl}^- / \text{K}^+$ in the ascending part of Henle's loop by blocking the ion carrier for these ions. The fractional sodium excretion can amount to 35% of the glomerularly filtrated sodium. Increased sodium excretion leads secondarily to increased urinary excretion and to increased distal-tubular K^+ -secretion attributable to osmotically bound water. The excretion of Ca^{2+} and Mg^{2+} ions is also increased. Besides the losses of the above-mentioned electrolytes, excretion of uric acid may be reduced, and a shift of the acidbase balance towards metabolic alkalosis may occur.

Furosemide interrupts the tubuloglomerular feedback mechanism at the macula densa, so that the saluretic efficacy is not attenuated.

Furosemide leads to dose-dependent stimulation of the renin-angiotensin-aldosterone system. In case of cardiac insufficiency, furosemide leads to an acute reduction of the cardiac preload through dilatation of the venous capacitance vessels. This early vascular effect seems to be mediated through prostaglandins and requires sufficient renal function with activation of the renin-angiotensin-aldosterone system as well as intact prostaglandin synthesis.

Furosemide has an antihypertensive effect as a consequence of increased excretion of sodium chloride and reduced responsiveness of vascular smooth muscle cells to vasoconstrictive stimuli, and a reduction in blood volume

5.2 Pharmacokinetic properties

Furosemide is a weak carboxylic acid which exists mainly in the dissociated form in the gastro-intestinal tract. Furosemide is rapidly but incompletely absorbed (60-70%) on oral administration and its effect is largely over within four hours. The optimal absorption site is the upper duodenum at pH 5.0. Regardless of route of administration, 69-97% of activity from a radio-labelled dose is excreted in the first 4 hours after the furosemide is given. Furosemide is bound to plasma albumin and little biotransformation takes place. Furosemide is mainly eliminated via the kidneys (80-90%); a small fraction of the dose undergoes biliary elimination and 10-15% of the activity can be recovered from the faeces.

a) In renal/hepatic impairment

Where liver disease is present, biliary elimination is reduced. Up to 50% renal impairment has little effect on the elimination rate of furosemide Tablets, but less than 20% residual renal function increases the elimination time.

b) The Elderly

The elimination of furosemide is delayed in the elderly where a certain degree of renal impairment is present.

c) New-born

A sustained diuretic effect is seen, possibly due to immature tubular function.

5.3 Preclinical safety data

Acute oral toxicity was low in all species tested. Chronic toxicity studies in the rat and dog led to renal alterations (among others fibrous degeneration and renal calcification).

In vitro and *in vivo* tests of genetic toxicology did not reveal any clinically relevant evidence of a genotoxic potential of furosemide.

Long-term studies in mice and rats did not yield any relevant evidence of a tumorigenic potential.

In studies of reproductive toxicology in foetal rats, a reduced number of differentiated glomeruli, skeletal anomalies of the scapulae, humerus and ribs (induced by hypokalaemia), as well as hydronephrosis occurred in foetal mice and rabbits after administration of high doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate Maize starch Pregelatinised maize starch

Sodium starch glycollate (Type A) Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage Blisters: Do not store above 25°C. Store in the original package. Tablet Containers: Do not store above 25°C. Keep the container tightly closed.

6.5 Nature and contents of container Al/ PVC/PVdC blister, pack sizes of 28, 30, 50, 56, 84, 98, 100 tablets. HDPE tablet containers, pack sizes of 100, 250, 500 and 1000 tablets Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirement.

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Ltd Unit 3, Canalside, Northbridge Road, Berkhamsted, Hertfordshire HP4 1EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

[PL 17907/0203](#) [PL 17907/0204](#)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/11/2011

10 DATE OF REVISION OF THE TEXT

15/11/2011

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

Please read all of this leaflet carefully before you start taking this medicine.

Keep the leaflet, you may need to read it again.

This medicine has been prescribed for you personally and you should not pass it on to others.

It may harm them, even if their symptoms are the same as yours.

If you have any further questions, please ask your doctor or pharmacist.

The name of this medicine is

FUROSEMIDE 20mg TABLETS BP or FUROSEMIDE 40mg TABLETS BP

The active ingredient in this medicine is furosemide. This is the new name for frusemide. The ingredient itself has not changed.

The tablets are available in two strengths and contain either 20 mg or 40 mg of the active ingredient furosemide. The tablets also contain lactose monohydrate, maize starch, pregelatinized maize starch, magnesium stearate and sodium starch glycolate.

The product licence holder and manufacturer is Bristol Laboratories Ltd., Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG UK.

What the tablets are and what they are used for

Furosemide belongs to a group of medicines called diuretics, which increase the amount of urine passed by the kidneys, helping to remove excess fluids from the body. Diuretics are also known as 'water tablets'.

Furosemide Tablets are used in the treatment of oedema (fluid retention) caused by disorders of the heart, kidneys or liver alone or in combination with other anti-hypertensive agents. The tablets may also be used to treat pulmonary oedema (build up of fluid in the lungs) and mild to moderate hypertension (high blood pressure).

Before you take the tablets

Do not take this medicine and tell your doctor if:

- you are allergic to Furosemide or any of the other ingredients in the tablets which are listed above.
- you are allergic to sulphonamides e.g. trimethoprim, sulfadiazine.
- you have been told that you have a low volume of fluid in your body or low blood pressure.
- you have difficulty in passing water for example because of an enlarged prostate gland (males only)
- you have problems with your liver or kidneys
- the patient is in pre-coma or coma state associated with liver disease.
- you have electrolyte deficiency (e.g. lower potassium or sodium levels)
- you are breast feeding

Check with your doctor or pharmacist before taking if:

- you have low blood pressure, your fluid electrolyte balance should be regularly monitored and the dose should be adjusted accordingly.
- you have diabetes (high blood sugar)
- you have gout (causes excessive uric acid in the blood and painful inflammation of the joints, mainly in the feet and hands and especially in the big toe)
- you have liver cirrhosis (tiredness, weakness, water retention, feeling or being sick, loss of weight or appetite, yellowing skin or eyes, itch)
- you have low level of protein in your blood (hypoproteinaemia)
- function of kidneys should be monitored regularly if the furosemide tablets are given to premature infants.
- you have been previously told by your doctor if you have intolerance to some sugars (such as lactose)

If you are taking furosemide for a long time your doctor may recommend you to have potassium rich diet (i.e. potatoes, bananas, tomatoes, spinach, dry fruits) or many also recommend a medical substitution of potassium.

Furosemide and other medicines that you may be taking sometimes affect each other's action.

Please speak to your doctor if you are taking any of the following:

- **drugs to lower blood pressure**, such as ACE inhibitors (e.g. captopril) or drugs like terfenadine used to prolong QT interval or any other anti-arrhythmic drugs.
- non-steroidal anti-inflammatory drugs (NSAIDs) e.g. ibuprofen or naproxen
- **digoxin** for your heart
- curariform **muscle relaxants** (eg vecuronium)
- **corticosteroids** used to treat allergic reactions
- **laxatives** used over a long period of time
- certain **treatments for asthma** such as theophylline
- **antibiotics** for infections that affect your kidneys or ears (eg cefaclor, colistin, gentamicin, vancomycin)
- **lithium** for depression or mania
- **aspirin** and related drugs (known as salicylates)
- **medicines to control diabetes** such as insulin or oral tablets
- **sucralate, cisplatin, phenytoin, carbamazepine, aminoglutethimide, carbenoxolone, liquorice, probenecid and methotrexate**

If you are going to have an operation you must tell the doctor you are taking furosemide.

This medicine contains lactose. If you have been told by your doctor that you have intolerance to some sugars (such as lactose), contact your doctor before taking this medicine.

This medicine may reduce mental alertness. Do not drive or operate machinery if it has this effect on you.

Pregnancy and breast feeding

Furosemide should only be used in pregnancy if indicated by your doctor or physician. Furosemide is likely to affect the production of milk in breast feeding mothers, therefore you may need to stop breast feeding for sometime if you are taking furosemide. Your doctor will provide further advice.

Taking your medicine

Take the tablets exactly as directed by your doctor. If you do not understand the directions, ask your pharmacist or doctor to explain them to you. The usual doses are detailed below. Doctors sometimes prescribe different doses to these and if this applies to you, discuss it with your doctor if you have not already done so. You should always follow your doctor's instructions as to how and when to take your medicine.

XXXXXX

Swallow the tablets whole with a drink of water before a meal or as instructed by your doctor.

Hypertension

The usual initial dose in adults is 20–40mg daily, adjusted if necessary until an effective response is achieved. In more severe cases doses of up to 60mg may be required per day.

Oedema caused by disorders of heart, liver or kidney:

The usual initial dose in adults is 20–40mg furosemide. If the diuretic response is not satisfactory the single dose can be doubled to 80mg after 6 hours. If there is still inadequate response an additional dose of 160mg may be given after further 6 hours.

The daily maintenance dose is usually 40–80mg.

In case of elderly patients, the dose may require adjustment in order to achieve a satisfactory response.

Children:

The usual dose is 1–2 mg per kg body weight daily. Maximum daily dose of 40 mg.

Take all of the tablets that have been prescribed for you, even if you begin to feel better. Your symptoms may start to improve before the condition is completely treated. If you stop taking the tablets too soon, your symptoms may return.

If you are taking the tablets for a long time and at a high dose your blood should be monitored regularly by your doctor, to check the levels of salts (electrolytes) are not becoming too low.

If you take too much:

If you, a child or someone else has taken too many tablets, contact your doctor or hospital casualty department immediately.

If you miss a dose:

Take the missed dose as soon as you remember, unless it is evening, in which case if you do take the missed dose you may need to get up in the night to pass water. Take your next dose at the usual time. Do not take a double dose to make up for the missed dose.

Possible Side Effects

As with all medicines there is a possibility of unwanted effects whilst taking this medicine, including:

- severe allergic reaction which may include a skin rash, itching, dermatitis, peeling skin, sensitivity to sunlight or sun lamps or fever
- inflammation of blood vessels (vasculitis, which may cause rash, fever and joint or muscle pains) or kidney inflammation, this may change the number of times you pass urine or you may see blood in your urine. You may have a fever, feel drowsy, or notice swelling e.g. of the ankles
- Pins and needles feeling on the skin (paraesthesia)
- **Altered balance of fluid or chemicals in the body** (e.g. sodium, potassium, chlorine and magnesium) causing a dry mouth, weakness, tiredness or drowsiness, restlessness, fits, muscle pain fatigue or cramps, low blood pressure, difficulty passing water, fast heart rate and feeling and being sick
- **Blood:** furosemide can occasionally cause changes in your blood; your doctor will perform regular blood tests to ensure no changes have occurred. The symptoms of these changes include anaemia, leading to tiredness and lethargy; unusual bleeding or bruising, blood slow to clot; ulcers in your throat, mouth or on your skin
- **Metabolism:** changes in levels of body chemicals (glucose, fats or calcium)
- **Stomach and intestines:** stomach irritation or feeling sick
- **Pancreas:** inflammation of the pancreas (pancreatitis) which may cause severe pains in your abdomen or back, nausea, vomiting and fever
- **Muscles and joints:** muscle tension
- **Urinary and genital:** kidney stones in premature babies
- **Senses:** hearing problems or ringing in your ears (tinnitus)
- **Other:** generally feeling unwell

If you notice any of the above side-effects, or you notice any other unusual or unexpected effects and think your tablets may be causing them, please inform your doctor or pharmacist.

Storing the tablets

Keep out of the reach and sight of children.

Blister: Do not store above 25°C. Store in the original package (blister carton).

Tablet Containers: Do not store above 25°C. Keep the container tightly closed.

Do not use the tablets after the expiry date as shown on the blister, label or carton. The expiry date refers to the last day of that month.

Unless your doctor tells you to, do not keep any tablets that you no longer need. Give them back to your pharmacist.

Further Information

What Furosemide Tablets look like and contents of the pack

- Furosemide 20mg tablets are round, white to off-white tablets marked 'F20' on one side and 'BL' on the other.
- Furosemide 40mg tablets are round, white to off-white, tablets marked 'F40' separated by a break line on one side and 'BL' on the other.
- The tablets are supplied in blister packs containing 28, 30, 50, 56, 84, 98 and 100 tablets and containers containing 100, 250, 500 & 1000 tablets.

Not all pack sizes may be marketed.

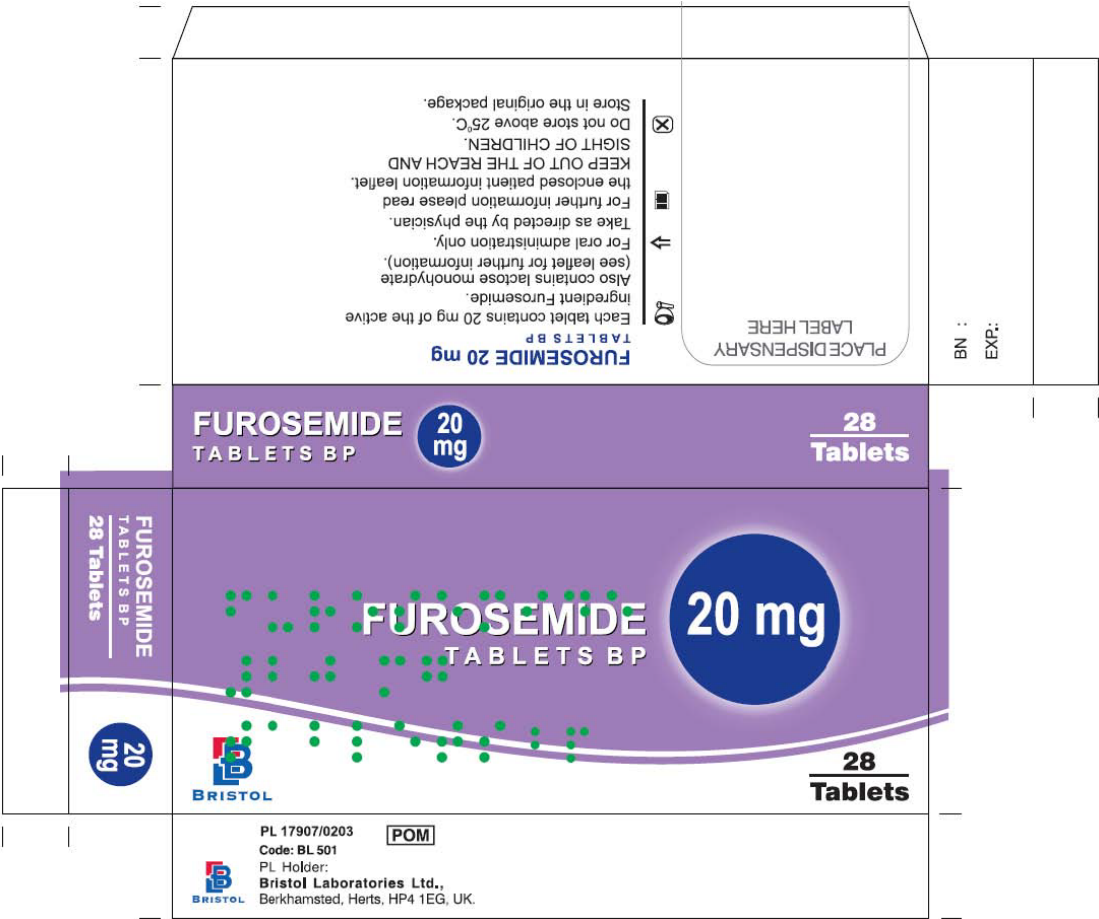
This leaflet was revised in January 2012.

PL 17907/0203 - Furosemide 20mg Tablets BP

PL 17907/0204 - Furosemide 40mg Tablets BP

LABELLING Furosemide 20 mg Tablets BP

Carton for blisters



Braille Blister foil HDPE container label Carton for blisters

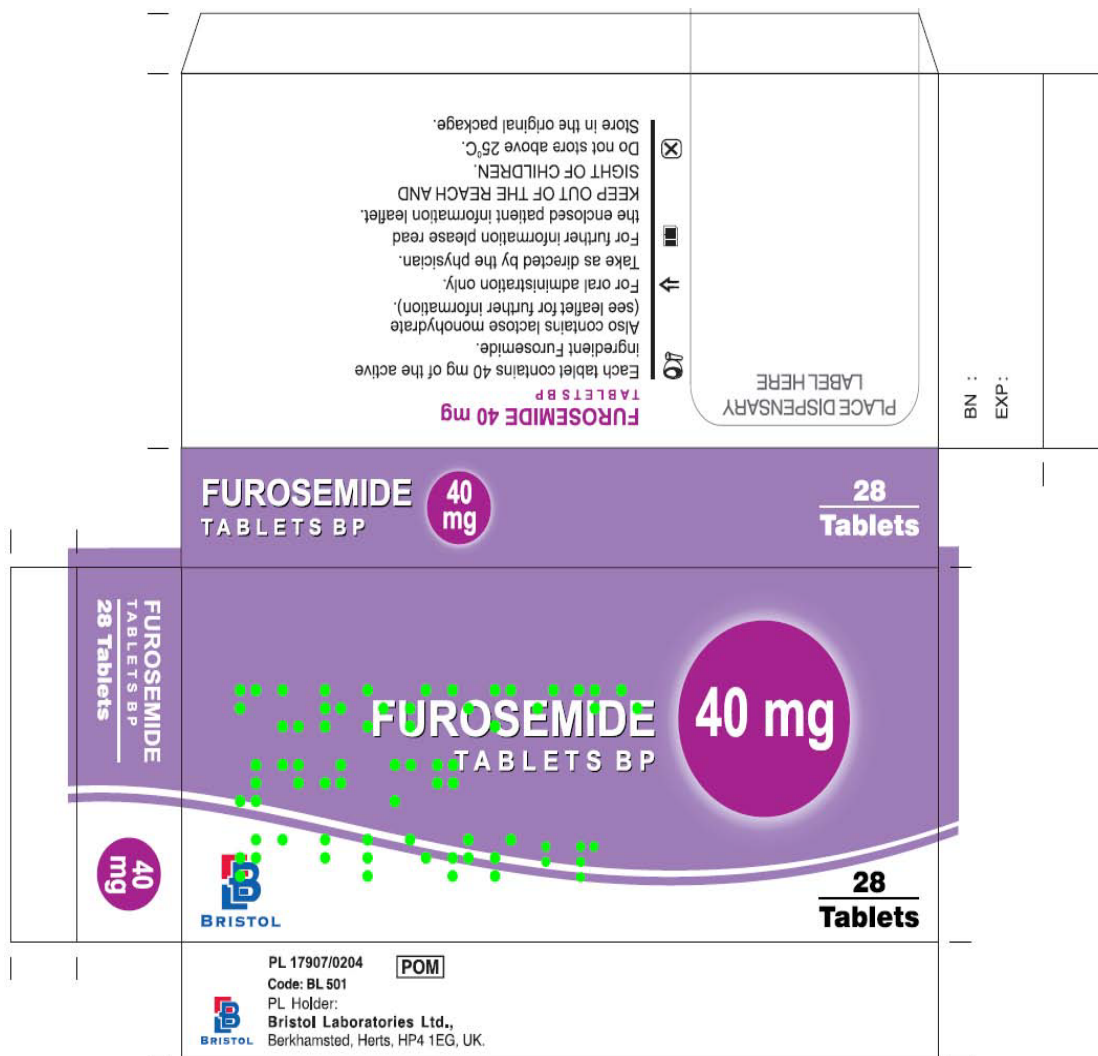
Furosemide

20mg

Tablets BP

Furosemide 40 mg Tablets BP

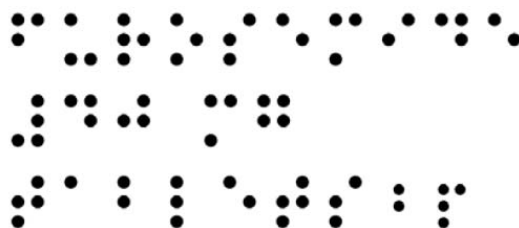
<p>Each tablet contains 20 mg of the active ingredient Furosemide. Also contains lactose monohydrate (see leaflet for further information). For oral administration only. Take as directed by a physician. For further information please read the patient information leaflet provided. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. Do not Store above 25°C. Keep the container tightly closed.</p>	 <p>FUROSEMIDE Tablets BP</p> <p>20 mg</p> <p>250 Tablets</p> <p></p>	<p>BN : EXP: Code: BL 501 POM PL 17907/0203 PL Holder: Bristol Laboratories Ltd Berkhamsted, Herts, HP4 1EG, UK.</p>
<p>Each tablet contains 20 mg of the active ingredient Furosemide. Also contains lactose monohydrate (see leaflet for further information). For oral administration only. Take as directed by a physician. For further information please read the patient information leaflet provided. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. Do not Store above 25°C. Keep the container tightly closed.</p>	 <p>FUROSEMIDE Tablets BP</p> <p>20 mg</p> <p>500 Tablets</p> <p></p>	<p>BN : EXP: Code: BL 501 POM PL 17907/0203 PL Holder: Bristol Laboratories Ltd Berkhamsted, Herts, HP4 1EG, UK.</p>
<p>Each tablet contains 20 mg of the active ingredient Furosemide. Also contains lactose monohydrate (see leaflet for further information). For oral administration only. Take as directed by a physician. For further information please read the patient information leaflet provided. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. Do not Store above 25°C. Keep the container tightly closed.</p>	 <p>FUROSEMIDE Tablets BP</p> <p>20 mg</p> <p>1000 Tablets</p> <p></p>	<p>BN : EXP: Code: BL 501 POM PL 17907/0203 PL Holder: Bristol Laboratories Ltd Berkhamsted, Herts, HP4 1EG, UK.</p>



Braille

Blister foil HDPE container label

Furosemide
40mg
Tablets BP



HDPE container label

<p>Each tablet contains 40 mg of the active ingredient Furosemide. Also contains lactose monohydrate (see leaflet for further information).</p> <p>For oral administration only.</p> <p>Take as directed by a physician.</p> <p>For further information please read the patient information leaflet provided.</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.</p> <p>Do not store above 25°C.</p> <p>Keep the container tightly closed.</p>	 <p>FUROSEMIDE 40 mg TABLETS BP</p>  <p>1000 Tablets</p>	<p>BN : EXP : Code BL 501 POM</p> <p>PL 17907/0204</p> <p>PL Holder: Bristol Laboratories Ltd., Berkhamsted, Herts, HP4 1EG, UK.</p>
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