ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bopediat 5 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 5 mg of furosemide.

Excipient with known effect
Each orodispersible tablet also contains sulphites.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet

Pale red, round, flat tablet with bevelled edge with 'F' debossed on one side and a score line on the other side with a diameter of 5.7 mm. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bopediat is indicated in children from birth to less than 18 years of age for the treatment of oedema of cardiac or renal origin, oedema of hepatic origin, and hypertension in patients with chronic kidney disease.

4.2 Posology and method of administration

Posology

The recommended daily dose of furosemide is 1 to 2 mg/kg of body weight, in 1 dose or 2 divided doses.

Dose should be adjusted according to the indication and severity of the disease.

Other pharmaceutical forms are available for administration to patients who cannot receive the relevant dose with a suitable number of orodispersible tablets.

Missed dose
If a dose is missed, the dose should be omitted and the next dose given as usual.

Method of administration

For oral use.

The tablet should be placed on the tongue or buccal cavity for all ages and allowed to disperse. Water may be consumed after the orodispersible tablet has fully disintegrated. Alternatively, for neonates, the tablet may be placed in the cheek pouch instead of on the tongue, however this may increase dispersion time.

Alternatively, Bopediat can be dispersed in tap water. Once dispersed, it can be administered orally via a dosing syringe. The amount of water required is 1 mL for every 2 tablets or part thereof (e.g. 1 mL for 2 tablets, 2 mL for 2.5 tablets, 3 tablets or 4 tablets). Sterile water should be used in children under

6 months of age. After administering Bopediat, the same volume of water used to prepare the dose should be drawn into the syringe and administered to the patient. This ensures the entire dose is delivered.

Bopediat orodispersible tablets have been designed with a functional score line. To ensure accurate administration of a half dose, the tablet should be held firmly and broken along the central score line, resulting in two equal halves.

This medicinal product can be administered with or without food.

Some patients may require administration via an enteral feeding tube, if they are unable to take the medicinal product orally.

For instructions on preparation of the medicinal product before administration via an enteral feeding tube, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Anuria or acute renal failure with anuria not responding to furosemide.
- Hepatic encephalopathy.
- Urinary tract obstruction.
- Hypovolaemia.
- Dehydration.
- Severe hypokalaemia.
- Severe hyponatraemia.
- Progressive hepatitis and severe hepatocellular insufficiency in patients on haemodialysis and in patients with severe renal failure (creatinine clearance less than 30 mL/min) due to the risk of accumulation of furosemide which is mainly excreted via the biliary route in this case.

4.4 Special warnings and precautions for use

Electrolyte balance

Serum sodium
Serum sodium levels should be checked before treatment is initiated, then at regular intervals. Any diuretic medicinal product can cause hyponatraemia, which can lead to neurological symptoms including confusion and seizures, increased risk of falls, worsening heart failure and hypotension and circulatory collapse (see section 4.8).

A decrease in serum sodium can initially be asymptomatic, therefore, regular monitoring is essential especially in those populations that are at risk.

Serum potassium
Potassium depletion with hypokalaemia is a major risk associated with loop diuretics (see section 4.8). Hypokalaemia (< 3.5 mmol/L) should be prevented in populations at risk i.e. malnourished patients and/or those receiving treatment with multiple medicinal products, those with cirrhosis along with oedema and ascites, with coronary heart disease or with heart failure. Hypokalaemia increases the cardiac toxicity of digitalis medicinal products and the risk of arrhythmia. In patients with prolonged QT interval (congenital or drug-induced), hypokalaemia promotes severe arrhythmias, particularly *torsades de pointes*, which can be potentially fatal, especially in patients with bradycardia. In all cases, plasma potassium levels should be monitored more frequently. The first plasma potassium assay should be performed during the week following treatment initiation.

Blood glucose
The hyperglycaemic effect of furosemide is moderate (see section 4.8). Blood glucose monitoring should be reinforced in diabetic and prediabetic patients.

Serum uric acid
The water and sodium depletion induced by furosemide reduces the urinary excretion of uric acid. In patients with hyperuricaemia, the incidence of gout attacks may be increased. Caution should therefore be exercised in patients with gout.

Serum creatinine
Furosemide can cause a transient elevation in creatinine (see section 4.8). Regular monitoring of serum creatinine is generally recommended during furosemide therapy.

Close monitoring is required of patients at risk of severe water-electrolyte imbalance (vomiting, diarrhoea, excessive perspiration, etc.). Dehydration, hypovolaemia and acid-base imbalance require corrective treatment and may require temporary treatment discontinuation.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with furosemide treatment (see section 4.8). At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions.
If signs and symptoms suggestive of these reactions appear, furosemide should be withdrawn immediately and an alternative treatment considered as appropriate. In children, the initial presentation of a rash can be mistaken for an infection and physicians should consider the possibility of a reaction to furosemide in children that develop symptoms of rash and fever during therapy with furosemide.

Photosensitivity

Photosensitivity reactions have been reported in patients using furosemide (see section 4.8).

If a photosensitivity reaction occurs during treatment, treatment should be discontinued. If re-administration is necessary, the patient should be advised to protect areas of skin exposed to the sun and artificial UVA rays.

Systemic lupus erythematosus

Exacerbation or activation of systemic lupus erythematosus (see section 4.8).

If activation or exacerbation of systemic lupus erythematosus occurs, then treatment with furosemide should be discontinued.

Hepatic disorders

In patients with hepatocellular insufficiency, treatment should be administered with caution and under strict monitoring of the water-electrolyte balance because there is a risk of hepatic encephalopathy (see section 4.8). If this occurs, treatment should be discontinued immediately.

Urinary tract obstruction

In patients with partial urinary tract obstruction, use of furosemide may lead to urinary retention (see section 4.8). Careful monitoring of urine output should therefore be instituted, particularly at the start of treatment with furosemide.

Dose adjustment or discontinuation

Furosemide treatment may require dose adjustment or discontinuation based on clinical judgement in patients with:

- Hypotension, especially in patients with a risk of cerebral or coronary ischemia, or other types of circulatory insufficiency.
- Symptomatic hypotension causing dizziness, fainting, or loss of consciousness may occur in some patients treated with furosemide, particularly in patients taking other medicinal products likely to cause hypotension (see section 4.5), and patients with other medical problems involving a risk of hypotension
- Hepatorenal syndrome (renal failure due to severe liver damage).
- Hypoproteinaemia, especially in patients with nephrotic syndrome: possible reduction in the diuretic effect of furosemide and potentiation of adverse reactions, especially ototoxicity.
- Cholelithiasis in premature infants receiving total parenteral nutrition concomitantly with furosemide
- Secondary hyperparathyroidism and bone disease in infants obtaining long-term furosemide treatment.

Paediatric population

Newborns and premature infants
In newborns and premature infants, prolonged use of furosemide at high doses carries a risk of nephrocalcinosis and/or intrarenal lithiasis. Renal ultrasonography is therefore recommended. Furosemide stimulates prostaglandin E2 synthesis, a potent dilator of the patent *ductus arteriosus*, and the administration of furosemide to any preterm infants should be carefully weighed against the risk of precipitation of a symptomatic patent *ductus arteriosus*.

Excipients with known effect

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium free’.

Sulphites
May rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Bopediat in the adult or paediatric population.

Potassium-depleting medicinal products

Hypokalaemia is a promoting factor for arrhythmia (*torsades de pointes* in particular) and increases the toxicity of certain medicinal products, for example digoxin. As a result, medicinal products that may induce hypokalaemia are involved in a large number of interactions. These agents include potassium-depleting diuretics, alone or in combination, stimulant laxatives, glucocorticosteroids, tetracosactide and amphotericin B (intravenous use). Serum potassium should be monitored more frequently if furosemide is co-administered with these medicinal products.

Digitalis glycosides

Hypokalaemia enhances the toxic effects of digitalis glycosides. Hypokalaemia should be corrected prior to treatment and clinical, electrolyte and electrocardiographic monitoring should be performed.

Potassium-sparing diuretics, alone or in combination (amiloride, potassium canrenoate, eplerenone, spironolactone, triamterene)

Although appropriate use of the medicinal product in combination with these agents may be useful in some patients, the possibility of hypokalaemia and, particularly in patients with renal failure and

diabetes, hyperkalaemia, cannot be ruled out. Blood potassium and, if necessary, electrocardiogram (ECG) monitoring are required. If needed, treatment may be reconsidered.

Sodium-depleting medicinal products

Certain medicinal products are more commonly involved in the onset of hyponatraemia. These include diuretics, desmopressin, serotonin reuptake inhibiting antidepressants, carbamazepine and oxcarbazepine. Combined use of these medicinal products increases the risk of hyponatraemia. Additional monitoring of serum sodium may be required.

Ototoxic medicinal products

Concomitant use of ototoxic medicinal products increases the risk of cochleovestibular damage. If this type of co-administration is necessary, monitoring of hearing should be reinforced. The medicinal products concerned are specifically glycopeptides such as vancomycin and teicoplanin, aminoglycosides, platinum compounds and loop diuretics.
Medicinal products causing nephrotoxicity and/or kidney injury

Some medicinal products increase the risk of nephrotoxicity or acute kidney injury. These include acetylsalicylic acid, aminoglycosides, angiotensin-converting enzyme (ACE) inhibitor. angiotensin II receptor blockers, iodinated contrast media, non-steroidal anti-inflammatory drugs (NSAIDs), platinum agents. Renal function should be monitored if these medical products are co-administered with furosemide. Dehydration and volume depletion increase the risk acute kidney injury. The patient's fluid balance should be monitored to ensure they are adequately hydrated.

Medicinal products causing hypotension

An enhanced hypotensive effect is possible with all antihypertensive medicinal products. For ACE inhibitors and angiotensin II receptor blockers consideration should be given to stopping the furosemide prior to their co-administration or starting with a lower dose of ACE inhibitor/ angiotensin II receptor blocker. In patients with congestive heart failure treated with diuretics, initial ACE inhibitor doses should be very low. Other medicinal products with an enhanced hypotensive effect, particularly orthostatic hypotension include: alpha-blockers, amifostine, baclofen, imipramine antidepressants, neuroleptics, nitrate derivatives. Blood pressure should be monitored in patients who are treated with co-administered medicinal products that can cause a hypotensive effect.

Medicinal products causing a reduction in the effect of furosemide

Aliskiren
Aliskiren reduces the plasma concentration of orally administered furosemide. A reduction in the effect of furosemide may be observed in patients treated with both aliskiren and oral furosemide, and it is recommended that the reduction in the diuretic effect be monitored and the dose of furosemide adjusted accordingly.

Phenytoin
The diuretic effect may be reduced by up to 50%. Higher doses of furosemide can be used.

Torsadogenic medicinal products

There is an increased risk of ventricular arrhythmias with torsadogenic medicinal products, especially *torsades de pointes*. Hypokalaemia should be corrected prior to treatment and clinical, electrolyte and electrocardiographic monitoring should be performed.

Torsadogenic medicinal products include:class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide) and class III antiarrhythmics (amiodarone, sotalol, ibutilide, dofetilide), certain phenothiazine neuroleptics (chlorpromazine, cyamemazine, fluphenazine, levomepromazine, pipotiazine), benzamides (amisulpride, sulpiride, sultopride, tiapride), butyrophenones (droperidol,

haloperidol, pipamrenone), other neuroleptics (pimozide, sertindole, flupentixol, zuclopenthixole), other medicinal products: bepridil, cisapride, diphemanil, dolasetron intravenous use, dronedarone, spiramycin intravenous use, erythromycin intravenous use, mizolastine, levofloxacin, halofantrine, lumefantrine, pentamidine, vincamine intravenous use, moxifloxacin, mequitazine, methadone, pracalopride, toremifene, arsenic compounds, citalopram, escitalopram.

Other medicinal products

Ciclosporin
There is a risk of elevated serum creatinine levels with no changes in ciclosporin plasma concentrations, even when there is no water/sodium depletion. In addition, there is a risk of hyperuricaemia and complications such as gout.

Lithium
Increased blood lithium can occur with signs of overdose, as is the case when patients follow a low-sodium diet with decreased urinary excretion of lithium. If co-administration cannot be avoided, strict monitoring of blood lithium and dose adjustment are required.

Metformin
Metformin-induced lactic acidosis can occur, caused by possible functional renal failure related to diuretics, particularly loop diuretics. Metformin should not be used if serum creatinine levels exceed age-appropriate levels.

Risperidone
In placebo-controlled studies conducted with risperidone in elderly patients (over 65 years of age) with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone. Caution should be exercised and the benefit/risk ratio of this combination or concomitant treatment with other potent diuretics should be considered prior to the decision to use.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of furosemide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Bopediat is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Furosemide/metabolites are excreted in human milk to such an extent that effects on the breastfed newborns/infants are likely.

Breast-feeding should be discontinued during treatment with Bopediat.

Fertility

No human data on the effect of furosemide on fertility are available.

4.7 Effects on ability to drive and use machines

Bopediat has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions are electrolyte imbalance (≥ 1/10), dehydration (≥ 1/10), hypovolaemia (≥ 1/10), increase in serum creatinine (≥ 1/10), increase in triglycerides (≥ 1/10) and orthostatic hypotension (≥ 1/10).

Tabulated list of adverse reactions

The following table lists the adverse reactions based on data from the literature on clinical studies in which furosemide was administered to 1 387 patients in total, all doses and indications combined.

The adverse reactions are listed in Table 1 below by MedDRA system organ class (SOC) and frequency, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 1 Adverse reactions

System organ class	Adverse reaction	Frequency
Blood and lymphatic system disorders	Haemoconcentration*	Common
	Thrombocytopenia	Uncommon
	Neutropenia	Rare
	Eosinophilia	Rare
	Agranulocytosis	Very rare
	Bone marrow failure	Very rare
Immune system disorders	Anaphylactic reactions	Rare
	Systemic lupus erythematosus	Not known
Metabolism and nutrition disorders	Electrolyte imbalance*	Very common
	Dehydration*,	Very common
	Hypovolaemia*	Very common
	Hyponatraemia*	Common
	Hypokalaemia*	Common
	Gout*	Common
	Metabolic alkalosis*	Not known
	Pseudo-Bartter syndrome*	Not known
Nervous system disorders	Hepatic encephalopathy*	Common
	Paraesthesia	Rare
	Dizziness	Not known
	Syncope, Loss of consciousness	Not known
	Headache	Not known
Ear and labyrinth disorders	Auditory disorder	Uncommon
	Deafness*	Uncommon
	Tinnitus	Rare
Vascular disorders	Orthostatic hypotension*	Very common
	Vasculitis	Rare
	Thrombosis*	Not known
	Nausea	Uncommon

Gastrointestinal disorders	Vomiting	Rare
	Diarrhoea	Rare
	Pancreatitis acute	Very rare
Hepatobiliary disorders	Cholestatic liver injury	Very rare
Skin and subcutaneous tissue disorders	Skin reaction	Uncommon
	Pruritus	Uncommon
	Urticaria	Uncommon
	Generalised bullous fixed drug eruption	Uncommon
	Pemphigoid	Uncommon
	Purpura	Uncommon
	Photosensitivity reaction	Uncommon
	Erythema multiforme	Uncommon
	Stevens-Johnson syndrome (see section 4.4)	Not known
	Toxic epidermal necrolysis (see section 4.4)	Not known
	Acute generalised exanthematous pustulosis (AGEP) (see section 4.4)	Not known
	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) (see section 4.4)	Not known
	Lichenoid keratosis	Not known
Musculoskeletal and connective tissue disorders	Rhabdomyolysis*	Not known
Renal and urinary disorders	Polyuria*	Common
	Tubulointerstitial nephritis	Rare
	Urinary retention*	Not known
	Nephrocalcinosis*	Not known
	Nephrolithiasis*	Not known
General disorders and administration site conditions	Pyrexia	Rare
Investigations	Blood creatinine increased*	Very common
	Blood triglycerides increased *	Very common
	Blood cholesterol increased*	Common
	Blood uric acid increased*	Common
	Carbohydrate tolerance decreased*	Uncommon
	Blood glucose increased*	Uncommon
	Transaminases increased	Very rare
	Blood urea increased*	Not known

* The adverse reactions marked with an asterisk are further described below.

Description of selected adverse reactions

Metabolism and nutrition disorders
Elevated blood glucose levels are sometimes observed, usually during high-dose, short courses of treatment. Reduced carbohydrate tolerance has been reported.

In diabetic patients, cases of uncontrollable blood glucose levels have been observed.

The following drug-induced adverse reactions may be observed and warrant treatment discontinuation or dose reduction: electrolyte imbalance, hypokalaemia, hyponatraemia, dehydration, hypovolaemia accompanied by orthostatic hypotension and metabolic alkalosis.

Electrolyte imbalance is promoted by the following: an overly strict low-sodium diet and certain disorders (e.g. cirrhosis, heart failure), combination with other medicinal products (see section 4.5), and gastrointestinal and nutritional disorders, which can worsen hypokalaemia in particular.

Hypokalaemia may or may not be associated with metabolic alkalosis. This tends to occur more readily with high doses or in cirrhotic, malnourished or heart failure patients (see section 4.4). Hypokalaemia may be particularly serious in patients with heart failure and may also cause severe arrhythmias, especially *torsades de pointes* which are potentially fatal, in particular when the medicinal product is administered in combination with quinidine anti-arrhythmic agents.

Pseudo-Bartter syndrome which includes hypokalaemia, hypochloraemia, alkalosis and hyperaldosteronism may occur if there is misuse and/or long-term use of the medicinal product.

Furosemide treatment can cause a transient elevation of serum creatinine, blood urea, as well as cholesterol and triglycerides. A slight increase in blood uric acid levels (approximately 10 to 30 mg/L) may occur during treatment and promote a gout attack.

Ear and labyrinth disorders
Auditory disorders and rare cases of tinnitus, generally transient, may occur, particularly in patients with renal impairment and hypoproteinaemia (nephrotic syndrome) (see section 4.4).

Cases of deafness, which may rarely be irreversible, have been reported after oral or intravenous administration of the medicinal product. Auditory disorders have been reported during concomitant administration with aminoglycoside antibiotics.

Vascular disorders
Hypovolaemia and dehydration may lead to haemoconcentration with a risk of thrombosis, particularly in elderly patients.

Hepatobiliary disorders
In patients with hepatocellular insufficiency, hepatic encephalopathy may occur (see sections 4.3 and 4.4).

Musculoskeletal and connective tissue disorders
Cases of rhabdomyolysis have been reported, usually in the context of severe hypokalaemia.

Renal and urinary disorders
Increased diuresis may cause or worsen urinary retention in patients with urinary tract obstruction and/or compression.

Cases of nephrocalcinosis and/or urinary calculus associated with hypercalciuria have been observed in very premature infants treated with high-dose injections of furosemide.

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 national reporting system listed in Appendix V.

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).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diuretics, sulfonamides, plain, ATC code: C03CA01

Mechanism of action

Saluretic activity
At usual therapeutic doses, the main effect of furosemide is on the ascending limb of the loop of Henle, where it inhibits chloride then sodium reabsorption. It has a secondary effect on the proximal tubule and dilution segment. Furosemide increases renal blood flow to the renal cortex. This property is of particular value when furosemide is used in combination with beta-blockers, which can have the opposite effect. Furosemide does not affect glomerular filtration (though increased glomerular filtration has been observed under certain circumstances). The saluretic activity increases dose-dependently and persists in patients with renal failure.

Antihypertensive activity and other effects
Furosemide has a hemodynamic effect characterised by reduced pulmonary capillary pressure even before any diuresis begins, and increases the storage capacity of the venous vascular bed as shown by plethysmography (these properties have been studied particularly via the intravenous route). Furosemide acts on all forms of water/sodium retention with a dose-dependent response. It has an antihypertensive effect resulting from both sodium depletion and its hemodynamic activity.

Paediatric studies

A randomised control study of 57 premature infants (≤ 2 000 gm) with respiratory distress syndrome who required mechanical ventilation after birth were randomised to furosemide (n=29) (1 mg/kg/day intravenously) vs control (n=27). A spontaneous increase in urine output occurred in the control group at 48 to 72 hours after the initiation of the study (mean -SD 7.0±3.5 hours postnatal age), along with a decrease in mean airway pressure for mechanical ventilation. The use of furosemide (7.3±3.5 hours postnatal age) enhanced urine output at 24 to 48 and 48 to 72 hours after administration, resulting in further decrease in mean airway pressure and facilitating extubation. There was, however, no significant difference between the groups with respect to incidence of patent *ductus arteriosus*, morbidity from bronchopulmonary dysplasia, and mortality.

A systematic review on intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease (CLD) concluded that in preterm infants < 3 weeks of age developing CLD, a single daily dose of furosemide improves oxygenation inconsistently. In patients > 3 weeks of age with CLD, pulmonary mechanics transiently improve in non-intubated patients after a single furosemide dose. Pulmonary mechanics and oxygenation improved in all patients after a week of treatment with furosemide.

5.2 Pharmacokinetic properties

Absorption

Furosemide is rapidly, though incompletely, absorbed from the gastrointestinal tract. Peak plasma concentrations are reached within approximately 60 minutes. Absorption from the gastrointestinal tract is slowed but not reduced by food.

The bioavailability of furosemide as an oral solution is 65%.

Distribution

Furosemide is 96 to 98% plasma protein bound (at therapeutic plasma concentrations). Protein binding is reduced in patients with liver failure.

The apparent volume of distribution is approximately 0.150 L/kg.

Biotransformation

A small amount of the absorbed furosemide is inactivated via hepatic, and most likely renal, glucuronide conjugation.

Elimination

The elimination half-life ($t^{1/2}$ beta) is approximately 50 minutes. Plasma clearance is approximately 2 to 3 mL/min/kg. This results from urinary and gastrointestinal elimination, partly via the biliary route. Furosemide is rapidly and predominantly excreted by the urinary route, mainly as unchanged medicinal product.

Furosemide crosses the placental barrier.

Furosemide is excreted in breast milk.

Special populations

Renal impairment
Bioavailability following oral administration is reduced. Biliary elimination compensates for renal failure and can reach 86% to 98% of the eliminated amount in anephric patients. Furosemide is poorly dialysable.

Paediatric population
Based on the predictions of a developed physiologically based pharmacokinetic (PBPK) model, no significant differences in the bioavailability of furosemide are expected between adults and paediatric population. Pre-term neonates have a larger volume of distribution and thus have an increased elimination half-life, which decreases with increasing post-natal age. Furosemide elimination can differ between paediatrics and adults, especially in neonates, due to differences in both size and renal development. One study reported half-lives of 19.9 and 7.7 hours in premature and full-term infants, respectively. The long half-life in newborns compared to adults is a function of both immature kidney function and an immature glucuronidation capacity.

5.3 Preclinical safety data

Animal studies have demonstrated a teratogenic effect. 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

Mannitol (E 421)
Maize starch
Croscarmellose sodium (E 468)
Povidone (E 1201)
Strawberry flavour (contains gum arabic (E 414), sodium, furaneol, sulphites (E 220), acetic acid (E 260))
Sodium stearyl fumarate
Iron oxide red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

12 months

6.4 Special precautions for storage

Do not store above 25 °C.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

PVC/PVDC/aluminium blister containing 28 orodispersible tablets.

Each carton contains 28, 56, 84 or 112 orodispersible tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Administration via an enteral feeding tube (nasogastric tube)

Bopediat orodispersible tablets disperse in tap water and can be administered via an enteral feeding tube (nasogastric tube) once dispersed. Sterile water should be used for administration to children under 6 months of age. Feeding tube studies with all standard feeding tube types (silicone, polyvinylchloride/PVC, polyurethane/PU) have shown that Bopediat can be administered without a blockage in tube sizes ranging from 4 Fr to 10 Fr when a dose of 60 mg was administered.

The number of required orodispersible tablets should be placed into a syringe (5, 10 or 20 mL syringe depending on number of tablets being administered), and the required amount of water drawn into the syringe: 1 mL for every 2 tablets or part thereof (e.g. 1 mL for 2 tablets, 2 mL for 2.5 tablets, 3 tablets or 4 tablets). The end of the syringe must be closed securely with a cap or held closed with a finger.

To disperse the tablets, the syringe needs to be turned upside down in a 180º movement by turning the wrist for at least 30 seconds (approximately 40 movements). A visual inspection needs to be performed to confirm complete dispersion. If necessary, the number of movements/time may be extended as needed to obtain a complete dispersion. When dispersed in water, the 5 mg tablets

produce a homogeneous pink solution. The final dispersed solution should be free from visible clumps or undissolved fragments.
Once dispersion is complete, the air needs to be removed from the syringe, after which the dose can be administered through the feeding tube. Following the administration of the medicinal product, the tube needs to be flushed with at least 5 mL of water for all tube types, except for 4 Fr tubes: in this case, the flush volume can be reduced to 3 mL.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Proveca Pharma Limited
2 Dublin Landings
North Wall Quay
Dublin 1
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2027/001
EU/1/26/2027/002
EU/1/26/2027/003
EU/1/26/2027/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Haupt Pharma Münster GmbH
Schleebrüggenkamp 15
48159 Münster
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON –5 mg orodispersible tablets

1. NAME OF THE MEDICINAL PRODUCT

Bopediat 5 mg orodispersible tablets
furosemide
For children from birth to less than 18 years

2. STATEMENT OF ACTIVE SUBSTANCE

Each orodispersible tablet contains 5 mg of furosemide.

3. LIST OF EXCIPIENTS

Contains sulphites.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablets

28 orodispersible tablets
56 orodispersible tablets
84 orodispersible tablets
112 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM THE MEDICINAL PRODUCTS.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Proveca Pharma Limited
2 Dublin Landings
North Wall Quay
Dublin 1
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2027/001 28 orodispersible tablets
EU/1/26/2027/002 56 orodispersible tablets
EU/1/26/2027/003 84 orodispersible tablets
EU/1/26/2027/004 112 orodispersible tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bopediat 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS – 5 mg orodispersible tablets

1. NAME OF THE MEDICINAL PRODUCT

Bopediat 5 mg orodispersible tablets
furosemide
For children from birth to less than 18 years

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Proveca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Bopediat 5 mg orodispersible tablets
furosemide

Read all of this leaflet carefully before you or your child starts taking this medicine because it contains important information for you or your child.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your or your child's doctor, pharmacist or nurse.
- This medicine has been prescribed for you or your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you or your child gets any side effects, talk to your or their doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Bopediat is and what it is used for

Bopediat contains the active substance furosemide. 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.

Bopediat is used in children from birth to less than 18 years of age for the treatment of:
- oedema (fluid retention) caused by heart, kidney or liver diseases, and
- hypertension (high blood pressure) associated with chronic (long-term) kidney disease.

The active substance in Bopediat, furosemide, blocks the reabsorption of sodium and chloride from a part of the kidneys known as the loop of Henle. This leads to increased production of urine, which helps remove excess fluid from the body and lowers blood pressure by reducing the volume of fluid in blood vessels.

2. What you need to know before you or your child takes Bopediat

Do not take Bopediat if you or your child
are allergic to furosemide or any of the other ingredients of this medicine (listed in section 6).
- have absence of urine production (anuria) or acute renal failure with anuria not responding to this medicine.
- have significant problems passing urine because of a blockage in the flow of urine (urinary tract obstruction).
- have a low volume of blood or other fluids circulating in your body (hypovolaemia).
- are dehydrated.
- have very low blood potassium levels (severe hypokalaemia) (see section 4, "Possible side effects").
- have very low blood sodium levels (severe hyponatraemia)

- have inflammation of the liver (hepatitis) that severely affects liver function and are either on haemodialysis (a procedure for removing waste products from the blood used in patients with kidney disease) or have severe kidney failure.
- have brain dysfunction caused by liver problems (hepatic encephalopathy).

Warnings and precautions
Talk to your or your child's doctor, pharmacist, or nurse before you or your child take Bopediat if you or your child:
- have pre-diabetes or diabetes (condition in which the body cannot adequately control blood sugar levels). Blood sugar levels should be checked regularly.
- have gout (too much uric acid in the blood). Treatment with Bopediat may make gout attacks more frequent.
- have problems with your liver as there is a risk of developing hepatic encephalopathy, a condition which can cause confusion, sleepiness, or unusual behaviour. Contact your doctor immediately if you notice any of these symptoms.
- have an urinary tract obstruction.
- have abnormal blood levels of sodium (salt), potassium or creatinine (a measure of kidney function).
- have low blood pressure.
- become dehydrated whilst taking Bopediat.
- have systemic lupus erythematosus (a condition in which the body's defence system attacks normal tissue causing symptoms such as swollen joints, tiredness and rashes). Treatment with Bopediat might make this worse.
- are taking other medical treatments which may cause a drop in blood pressure or have other medical problems involving a risk of a decrease in blood pressure.
- are pregnant.
- seek medical help immediately if you get a severe rash, blisters, peeling skin, mouth or eye sores, swelling of the face or tongue, fever, or feel very unwell (severe cutaneous adverse reaction, SCARs).
- have hepatorenal syndrome (a serious condition where kidney function worsens due to severe liver disease).
- have low levels of protein in the blood (hypoproteinaemia).
- are a premature baby with gallstones (cholelithiasis).
- are an infant with secondary hyperparathyroidism (overactive parathyroid glands due to another condition) or bone disease.

During treatment, your or your child's doctor will organise medical check-ups and blood tests to monitor how your or your child's treatment is going. Treatment may need to be stopped for a short time, or the dose reduced, if you become dehydrated, lose too much fluid, or your body's chemical balance is disturbed (e.g. low potassium or sodium levels).

Exposure to the sun or UV rays: tell your doctor if you or your child's skin reacts strongly (such as reddens, burns, or blisters more easily than usual) after exposure to the sun or UV rays (photosensitivity), because your treatment may have to be stopped.

When taking this medicine, you or your child should limit exposure to sunlight and UV rays, avoid sunbeds, wear protective clothing when outdoors, and use a high sun protection factor (SPF) sunscreen. If a skin reaction occurs, contact your doctor.

If you are not sure if any of the above apply to you or your child, talk to your doctor, pharmacist or nurse before taking Bopediat.

Newborns and premature infants
Use of Bopediat in newborns and premature infants should be carefully monitored by a doctor, pharmacist or nurse.

In premature infants, this medicine may increase the risk of a heart condition called patent *ductus arteriosus* (a blood vessel near the heart that stays open when it should have closed after birth). Your doctor will carefully consider the benefits and risks before giving this medicine and monitor your baby during treatment.

If this medicine is used in newborns and premature infants, long-term use of this medicine at high doses may require ultrasound scans of the kidneys.

Other medicines and Bopediat
Tell your doctor or pharmacist if you or your child is taking, has recently taken, or might take any other medicines.

Tell your doctor if you or your child is taking:
- Medicines that can lower the levels of potassium in the blood, such as water tablets (diuretics), corticosteroids, tetracosactide, amphotericin B, and certain laxatives;
- Medicines that can lower the levels of sodium in your blood, such as diuretics, desmopressin, certain antidepressants, carbamazepine and oxcarbazepine;
- Medicines that may affect your hearing (such as vancomycin, teicoplanin, aminoglycosides, platinum compounds and loop diuretics);
- Blood pressure-lowering medicines, including digitalis medicinal products, diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and alpha-blockers;
- Medicines containing ciclosporin used as an immunosuppressant;
- Medicines containing phenytoin used to treat epilepsy;
- Diabetes medicines such as metformin;
- Medicines used to treat behaviour or mental health conditions (such as risperidone);
- Medicine used to treat mood disorders such as bipolar disorder (lithium);
- Medicines that may cause a type of heart rhythm disorder called *torsades de pointes*. These include:
    - Some antidepressants (such as citalopram, escitalopram),
    - Some medicines used to treat mood and behaviour disorders (such as phenothiazines [chlorpromazine, cyamemazine, fluphenazine, levomepromazine, pipotiazine, mequitazine], benzamides [amisulpride, sulpiride, sultopride, tiapride], butyrophenones [droperidol, haloperidol, pipamperone], pimozide, sertindole, flupentixol, zuclopenthixol),
    - Some antibiotics from the macrolide group (such as spiramycin (into a vein) erythromycin into a vein) or the fluoroquinolone group (such as moxifloxacin, levofloxacin),
    - Some medicines used to treat cancer and its side effects (such as toremifene, arsenic compounds, and dolasetron into a vein),
    - Some medicines used to treat malaria (such as halofantrine, lumefantrine),
    - Some medicines used to treat infections caused by fungi or parasites (such as pentamidine),
    - Some medicines used to treat constipation (such as cisapride, prucalopride),
    - some medicines used to treat heart rhythm disorders (such as quinidine, hydroquinidine disopyramide, dofetilide, amiodarone, sotalol, ibutilide, dronedarone),
    - Bepridil (a medicine used to treat angina pectoris (chest pain)),
    - Vincamine into a vein (a medicine used to treat minor neurological disorders related to age),
    - Methadone (a medicine used to treat drug addiction) (see section "Warnings and precautions").
- Medicines that may cause nephrotoxicity and/or kidney injury when taken with furosemide, e.g.:
    - Medicines containing aminoglycosides (a type of antibiotic drugs);
    - ACE inhibitors or angiotensin II receptor blockers (for high blood pressure);
    - Non-steroidal anti-inflammatory drugs and acetylsalicylic acid (aspirin);
    - Medicines containing iodinated contrast agents for diagnostic purposes;

    - Medicines containing platinum compounds, used to treat some types of cancer.
- Medicines that may cause hypotension when taken with furosemide, e.g.:
    - Alpha-blockers (for high blood pressure);
    - Medicines containing baclofen (a medicine used to treat involuntary muscle contractions);
    - Medicines containing nitrate derivatives and related compounds for chest pain (*angina pectoris*);
    - Imipramine antidepressants and neuroleptics (for mental diseases);
    - Medicines containing amifostine (medicines used to treat cancer).

Your doctor may have to change your or your child's dose and/or take other precautions if you or your child is taking the following medicine:
- Aliskiren, used to treat high blood pressure.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

There are no or limited amount of data from the use of furosemide in pregnant women. Studies in animals have shown reproductive toxicity.

Bopediat is not recommended during pregnancy and in women of childbearing potential not using contraception.

Furosemide/metabolites are excreted in human milk to such an extent that effects on the breastfed newborns/infants are likely. Breast-feeding should be discontinued during treatment with Bopediat.

Driving and using machines
Bopediat has no or negligible influence on the ability to drive and use machines.

Bopediat contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Bopediat contains sulphites
May rarely cause severe hypersensitivity reactions and bronchospasm.

3. How to take Bopediat

Always take this medicine exactly as your or your child's doctor or pharmacist has told you. Check with the doctor or pharmacist if you are not sure.

The number of tablets you or your child need to take will depend on your or your child's body weight and as well as the reason for and severity of the illness being treated.

The recommended daily dose is 1 to 2 mg/kg of body weight, given as a single dose or as two divided doses.

Bopediat should be taken by mouth.

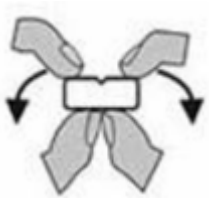
The tablet can be taken with or without food.

This medicine comes as an orodispersible tablet, which means it dissolves in the mouth. Place the tablet on the tongue or in the buccal cavity (the space inside the mouth between the cheeks and teeth) and allow it to disperse. A small drink of water may be taken after the tablet has fully disintegrated.

Alternatively, for newborns, the tablet may be placed in the cheek pouch instead of on the tongue, but this may increase how long the tablet takes to dissolve.

Alternatively, Bopediat can be dispersed in tap water. Once dispersed, it can be also given via a dosing syringe. The amount of water required is 1 mL for every 2 tablets or part thereof (e.g. 1 mL for 2 tablets, 2 mL for 2.5 tablets, 3 tablets or 4 tablets). Boiled and cooled water should be used in children under 6 months of age. After administering Bopediat, draw into the syringe the same volume of water used to prepare the dose and administer it to the patient. This ensures the entire dose is delivered.

Bopediat orodispersible tablets have been designed with a functional score line (dividing mark). In order to accurately give half a tablet, hold the tablet firmly and break it down the central score line. The tablet will divide into two equal halves.



Some patients may need to be given Bopediat through a feeding tube (nasogastric tube, tube sizes ranging from 4 Fr to 10 Fr) that goes directly into the stomach. Bopediat disperses in tap water and once dispersed it can be given through a feeding tube according to the instructions below. Boiled and cooled water should be used in children under 6 months of age.

1. Place the number of required Bopediat orodispersible tablets into a syringe (5, 10 or 20 mL syringe depending on number of tablets to be given).

2. Draw the required amount of water into the syringe: 1 mL for every 2 tablets or part thereof (e.g. 1 mL for 2 tablets, 2 mL for 2.5 tablets, 3 tablets or 4 tablets).

3. Make sure the end of the syringe is closed securely with a cap or held closed with a finger.

4. To disperse the tablets, turn the syringe upside down in a 180 ° movement by turning the wrist for at least 30 seconds (approximately 40 movements). Visually check if the tablets have been completely dissolved and if not, extend the number of movements/time as needed to obtain a complete dispersion.

5. Remove air from the syringe and apply the dose to the feeding tube. After giving the dose, flush the tube with water:
   - 3 mL for very small tubes (4 Fr)
   - 5 mL for all other tube sizes (5-10 Fr)

If you or your child takes more Bopediat than they should
Do not give more medicine than your or your child’s doctor tells you to. If you or your child has swallowed more tablets than the doctor has prescribed, tell your doctor immediately or contact your nearest hospital casualty/accident and emergency department even if there are no signs of discomfort. Take the medicine in its original package with you to enable the doctor to identify your medicine easily.

Possible signs of taking too much of this medicine include:
- Passing a lot of urine or feeling very thirsty
- Fast heartbeat
- Feeling weak, faint or lightheaded
- Drowsiness, confusion or unusual sleepiness

- Muscle weakness or floppy limbs
- Very low blood pressure
- Sudden kidney failure
- Blood clots.

If you or your child forgets to take Bopediat
If you or your child forgets to take Bopediat, skip the missed dose. Take the next dose as usual. Do not take a double dose to make up for a forgotten dose.

If you or your child stops taking Bopediat
Do not stop taking or giving Bopediat unless your or your child's doctor tells you to.

If you have any further questions on the use of this medicine, ask your or your child's doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using Bopediat and seek medical attention immediately if you notice any of the following symptoms:
- Reddish non-elevated, target-like or circular patches on the skin of the trunk, often with central blisters, skin peeling, ulcers of the mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms. These may be signs of conditions named Stevens-Johnson syndrome (frequency not known) or toxic epidermal necrolysis (frequency not known).
- Widespread rash, high body temperature and enlarged lymph nodes. These may be signs of a life-threatening condition called DRESS (drug reaction with eosinophilia and systemic symptoms). The frequency of this side effect is not known.
- A red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The symptoms usually appear at the start of treatment and may be signs of a condition called acute generalised exanthematous pustulosis (frequency not known).
- Sudden severe allergic reaction with breathing difficulty, swelling to the tongue/lips, light-headedness, fast heartbeat, sweating and loss of consciousness (anaphylactic reactions). The frequency of this side effect is rare.

Other possible side effects

Very common (may affect more than 1 in 10 people)
- Decrease in the total amount of fluid in the body (hypovolaemia). Signs of hypovolaemia include feeling dizzy or lightheaded, feeling very thirsty, reduced urine output and cool clammy skin.
- A marked drop in blood pressure when moving from a sitting to a standing position (orthostatic hypotension), which may be accompanied by dizziness and/or faintness.
- Increase in creatinine in the blood which can be a sign of worsening kidney problems (blood creatinine increased).
- Increase in fats (triglycerides) in the blood (blood triglycerides increased).
- Changes in the amount of salts and water in your body (electrolyte imbalance).
- Loss of too much water from your body (dehydration).

Common (may affect up to 1 in 10 people)
- Brain problems e.g. confusion, drowsiness, caused by liver problems (hepatic encephalopathy).
- High levels of uric acid in the blood (blood uric acid increased), which may lead to physical symptoms such as painful inflammation in the joints (gout).

- Increase in cholesterol in the blood (blood cholesterol increased).
- Low blood potassium levels (hypokalaemia).
- Low blood sodium levels (hyponatraemia).
- Production of excessive amounts of urine (polyuria).
- A condition where the blood becomes more concentrated due to loss of fluid (haemoconcentration).

Uncommon (may affect up to 1 in 100 people)
- Skin reactions which may be allergic or non-allergic (skin reaction).
- Itchy rash which is raised or bumpy (urticaria).
- An autoimmune disorder that causes blisters in the skin and moist body surfaces (pemphigoid).
- An allergic reaction that causes widespread, blistering sores on the skin (generalised bullous fixed drug eruption).
- Itching (pruritus).
- Sunburn-like reactions following exposure to the sun or UV radiation (photosensitivity).
- A skin reaction that causes red spots or patches on the skin, that may look like a target or "bulls-eye" with a dark red centre surrounded by paler red rings (erythema multiforme).
- Little reddish-purple patches on the skin (purpura).
- Feeling sick (nausea).
- Impairment of hearing (auditory disorder).
- Deafness (which may be irreversible).
- Impaired ability to control blood sugars (carbohydrate tolerance decreased).
- An increase in blood sugars (blood glucose increased).
- Low levels of blood platelets, components that help the blood to clot (thrombocytopenia).

Rare (may affect up to 1 in 1 000 people)
- Fever (pyrexia).
- An excess of eosinophils, a type of white blood cell (eosinophilia).
- Low levels of neutrophils, a type of white blood cell that fights infection (neutropenia).
- Sensation like numbness, tingling, pins and needles (paraesthesia).
- Vomiting.
- Diarrhoea.
- A kidney disorder in which there is inflammation within the kidneys that affects their ability to filter blood and make urine (tubulointerstitial nephritis).
- Ringing or buzzing in the ears (tinnitus).
- Inflammation of the blood vessels (vasculitis).
- Sudden swelling of the face, lips, tongue or throat, difficulty breathing or swallowing, severe itching or rash (anaphylactic reaction).

Very rare (may affect up to 1 in 10 000 people)
- Sudden inflammation of the pancreas causing severe pain the belly and back (pancreatitis acute).
- Liver damage due to the build-up of bile, a fluid made in the liver that helps to breakdown fats (cholestatic liver injury).
- Increase in levels of liver enzymes as seen in blood tests (transaminases increased).
- Very low level of a type of white blood cell called granulocytes which are important to fight infection (agranulocytosis).
- A condition where the bone marrow stops making blood cells (bone marrow failure).

Not known (frequency cannot be estimated from the available data)
- Formation of blood clots in the blood vessels (thrombosis).
- Difficulty releasing urine from the bladder (urinary retention).
- Kidney stones (nephrolithiasis).
- Build-up of calcium in the kidneys (nephrocalcinosis).

- Increase in urea in the blood (blood urea increased).
- Decrease in the amount of potassium in the blood associated with a decrease in chloride in the blood and an acid-base imbalance, together with an increase in aldosterone secretion (pseudo-Bartter syndrome).
- A change in the acid-base balance in the blood (metabolic alkalosis).
- An inflammatory, connective tissue disease that can affect the joints and many organs, including the skin, heart, lungs, kidneys, and nervous system (systemic lupus erythematosus).
- Dizziness.
- Fainting (syncope).
- Loss of consciousness.
- Headache.
- Breakdown of muscles often leading to kidney damage (rhabdomyolysis).
- A non-cancerous, raised skin lesion that may itch or change colour (lichenoid keratosis).
- A widespread rash with small pus-filled bumps, often with fever (Acute generalised exanthematous pustulosis (AGEP)).
- A severe rash with blistering of the skin, mouth, eyes or genitals (Stevens-Johnson syndrome (SJS)).
- A rash with fever, swollen glands and possible effects on internal organs such as the liver, kidneys or lungs (Drug reaction with eosinophilia and systemic symptoms (DRESS)).
- Peeling of large areas of skin (Toxic epidermal necrolysis (TEN)).

Reporting of side effects
If you or your child gets any side effects, talk to your or your child's doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Bopediat

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after 'EXP'. The expiry date refers to the last day of that month.

Do not store above 25 °C.
Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Bopediat contains
- The active substance is furosemide.
  Bopediat 5 mg orodispersible tablets contain 5 mg of furosemide.
- The other excipients are:

mannitol (E 421), maize starch, croscarmellose sodium (E 468), povidone (E 1201), strawberry flavour (contains gum arabic (E 414), sodium, furaneol, sulphites (E 220), acetic acid (E 260)) (see section 2 'Bopediat contains sulphites'), sodium stearyl fumarate (see section 2 'Bopediat contains sodium'), iron oxide red (E 172).

What Bopediat looks like and contents of the pack

Bopediat 5 mg orodispersible tablets are pale red, round, flat with bevelled edge with ‘F’ debossed on one side and a score line on the other side with a diameter of 5.7 mm. The tablet can be divided into equal doses.

Bopediat 5 mg orodispersible tablets are available in PVC/PVDC/aluminium blisters containing 28 tablets each.

Each carton contains 28, 56, 84 or 112 orodispersible tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Proveca Pharma Limited
2 Dublin Landings
North Wall Quay
Dublin 1
Ireland

Manufacturer
Haupt Pharma Münster GmbH
Schleebrüggenkamp 15
48159 Münster
Germany

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.