# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Bendroflumethiazide 2.5 mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Bendroflumethiazide 2.5mg.
Excipient with known effect: Also contains 60 mg of lactose.
For the full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Tablet
White to almost white circular, biconvex, uncoated tablets

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

For the treatment of oedema and hypertension. Bendroflumethiazide may also be used to suppress lactation.

### 4.2 Posology and method of administration

Posology
Adults:

Oedema:

Initially, 5-10 mg in the morning, daily or on alternate days; maintenance dose 5-10 mg one to three times weekly.

Hypertension:

The usual dose is 2.5 mg taken in the morning. Higher doses are rarely necessary.

Suppression of lactation:

5 mg in the morning and 5 mg at midday for about five days.

Children:

Dosage in children may be up to 400 mcg/kg bodyweight initially, reducing to 50-100 mcg/kg bodyweight daily for maintenance.

Elderly:

The dosage of thiazide diuretics may need to be reduced in the elderly, particularly when renal function is impaired, because of the possibility of electrolyte imbalance.

Method of administration

For oral administration

### 4.3 Contraindications

- Hypersensitivity to the active substance, other thiazides, or to any of the excipients listed in section 6.1

- Refractory hypokalaemia, hyponatraemia, or hypercalcaemia
- Severe renal and hepatic insufficiency
- Symptomatic hyperuricaemia
- Addison's disease

**4.4 Special warnings and precautions for use**

Bendroflumethiazide may raise serum uric acid levels with consequent exacerbation of gout insusceptible patients. Bendroflumethiazide should be used with caution in patients with mild to moderate hepatic or renal impairment (avoid if severe). Renal function should be continuously monitored during thiazide therapy. Thiazide diuretics may exacerbate or activate systemic lupus erythematosus in susceptible patients.

All thiazide diuretics can cause electrolyte imbalance, especially in patients with renal or hepatic impairment or in those receiving higher or prolonged doses. Serum electrolytes should be checked for abnormalities, particularly hypokalaemia, and the latter corrected by the addition of a potassium supplement to the regimen. Aggravates diabetes mellitus and gout; increased risk of hypomagnesaemia in alcoholic cirrhosis.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Regular ongoing monitoring and blood tests are to be performed in elderly patients and patients who are on long term treatment with bendroflumethiazide.

**Choroidal effusion, acute myopia and secondary angle-closure glaucoma:**
Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

This product contains the excipient lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**4.5 Interaction with other medicinal products and other forms of interaction**

Sensitivity to digitalis glycosides may be increased by the hypokalaemic effect of concurrent bendroflumethiazide. Patients should be observed for signs of digitalis intoxication, in particular arrhythmias, and if these appear, the dosage of the digitalis glycoside should be temporarily reduced and a potassium supplement given to restore stability.

Serum lithium concentrations may be increased by concurrent use of thiazide diuretics.

Non-steroidal anti-inflammatory agents may blunt the diuretic and antihypertensive effects of thiazide diuretics. Diuretics may increase the risk of nephrotoxicity of NSAIDs.

Xanthines, beta-agonists, ACTH, corticosteroids, acetazolamide and carbenoxolone may exacerbate the hypokalaemia associated with thiazide use. Thiazide diuretics may enhance the neuromuscular blocking effects of the non-depolarising muscle relaxants, e.g. tubocurarine.

Thiazides may enhance the effects of antihypertensive agents, while postural hypotension associated with therapy may be enhanced by concomitant ingestion of alcohol, barbiturates or opioids.

Concomitant use of carbamazepine may increase the risk of hyponatraemia.

There is an increased risk of hyponatraemia if thiazides are given with amphotericin.

The risk of hypercalcaemia is increased by the concomitant intake of calcium salts or vitamin D preparations.

Concomitant use with cisplatin can lead to an increased risk of nephrotoxicity and ototoxicity.

The cardiac toxicity of disopyramide, amiodarone, flecainide and quinidine is increased if hypokalaemia occurs. The action of lidocaine and mexiletine is antagonised by hypokalaemia.

There is an increased risk of hyponatraemia when thiazides are used concomitantly with aminoglutethimide. Thiazides can cause an increased risk of hypercalcaemia with toremifene.

Colestipol and colestyramine may reduce the absorption of thiazide diuretics and should therefore be given 2 hours prior to, or after the ingestion of bendroflumethiazide.

Calcium-channel blockers and moxisylyte can cause an enhanced hypotensive effect.

There is an increased risk of postural hypotension with tricyclic antidepressants. There may also be an increased risk of hypokalaemia if thiazides are given with reboxetine. Concomitant use with monoamine oxidase inhibitors (MAOIs), baclofen or tizanidine may also give an increased hypotensive effect.

Oestrogens and combined oral contraceptives may antagonise the diuretic effect of thiazides.

There is an increased risk of first-dose hypotensive effect of post-synaptic alpha-blockers such as prazosin.

Hypokalaemia increases the risk of ventricular arrhythmias with pimozide or thioridazine, therefore, concomitant use should be avoided. Hypokalaemia or other electrolyte imbalance also increases the risk of ventricular arrhythmias with terfenadine.

Bendroflumethiazide may interfere with a number of laboratory tests, including estimation of serum protein-bound iodine and tests of parathyroid function.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**
Diuretics (bendroflumethiazide) are best avoided for the management of oedema of pregnancy or hypertension in pregnancy as their use may be associated with hypokalaemia, increased blood viscosity and reduced placental perfusion.

There is insufficient evidence of safety in human pregnancy and foetal bone marrow depression and thrombocytopenia and neonatal jaundice have been described.

**Breast-feeding**
As diuretics pass into breast milk and Bendroflumethiazide can suppress lactation, its use should be avoided in mothers who wish to breast feed.

**4.7 Effects on ability to drive and use machines**

No adverse effects known.

**4.8 Undesirable effects**

The following undesirable effects, which are listed in system order class, have previously been associated with Bendroflumethiazide. Specific frequencies for the occurrence of these effects are not available.

*Blood and lymphatic system disorders:*
Rarely, blood dyscrasias including agranulocytosis, aplastic anaemia, neutropenia, thrombocytopenia (neonatal thrombocytosis is reported when given in late pregnancy) and leucopenia have been reported.

*Immune system disorders:*
Hypersensitivity reactions

*Metabolism and nutrition disorders:*
Bendroflumethiazide may lower carbohydrate tolerance and the insulin dosage of some diabetic patients may require adjustment.

Care is required when bendroflumethiazide is administered to patients with a known predisposition to diabetes (hyperglycaemia reported).
Bendroflumethiazide may raise serum uric acid levels and exacerbate gout in susceptible individuals (hyperuricaemia). Plasma lipids may be altered in patients taking bendroflumethiazide. Hypercalcaemia is also reported with unknown frequency.

*Cardiac and vascular disorders*:
Postural hypotension

*Respiratory, thoracic and mediastinal disorders:*
Pneumonitis, pulmonary oedema

*Gastrointestinal disorders:*
Nausea, vomiting, diarrhoea, constipation and gastric irritation have all been reported

*Hepatobiliary disorders:*
Pancreatitis, intrahepatic cholestasis

*Skin and subcutaneous tissue disorders:*
Rash (including exfoliative dermatitis), photosensitivity, severe skin reactions also reported

*Reproductive system and breast disorders:*
Impotence (reversible on discontinuing the drug)

*Investigations:*
Hypokalaemia, hypomagnesaemia, hyponatraemia, hypochloraemic alkalosis. Hypokalaemia may result in polyuria, malaise, muscle weakness or cramp, dizziness, nausea, anorexia or vomiting

***Description of selected adverse reactions*:**
Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

**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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

**4.9 Overdose**

Symptoms of overdosage include anorexia, nausea, vomiting, diarrhoea, diuresis, dehydration, hypotension, dizziness, weakness, muscle cramps, paraesthesia, tetany, gastrointestinal bleeding, hyponatraemia, hypo- or hyperglycaemia, hypokalaemia and metabolic alkalosis. Initial treatment consists of either emesis or gastric lavage, if appropriate. Otherwise treatment should be symptomatic and supportive including the correction of fluid and electrolyte imbalance.
Blood pressure should also be monitored.
There is no specific antidote.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: diuretic, ATC code: C03AA01

Bendroflumethiazide is a thiazide diuretic which reduces the absorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium and chloride ions, and consequently of water. The excretion of other electrolytes, notably potassium and magnesium, is also increased.

The excretion of calcium is reduced. Thiazides also reduce carbonic anhydrase activity so that bicarbonate excretion is increased, but this effect is generally small and does not appreciably alter the acid base balance or the pH of the urine. Thiazides also have a hypotensive effect, due to a reduction in peripheral resistance and enhance the effects of other antihypertensive agents.

**5.2 Pharmacokinetic properties**

*Absorption:* Bendroflumethiazide has been reported to be completely absorbed from the gastrointestinal tract and it is fairly extensively metabolised. Diuresis is initiated in about 2 hours and lasts for 12-18 hours or longer. About 30% is excreted unchanged in the urine. The onset of the hypotensive action is generally three or four days.

*Distribution:* Bendroflumethiazide is more than 90% bound to plasma proteins.

*Metabolism:* There are indications that it is fairly extensively metabolised. Peak plasma levels are reached in 2 hours and a plasma half- life of between 3 and 8.5 hours on average.

*Elimination:* About 30% is excreted unchanged in the urine with the remainder excreted as uncharacterized metabolites.

**5.3 Preclinical safety data**

Not applicable.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Lactose
Talc
Pregelatinised starch
Stearic acid

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

Do not store above 25ºC

**6.5 Nature and contents of container**

PVC/PVDC Aluminium foil blisters, available in pack sizes of 14, 28, 56, 84 tablets.
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements

**7 MARKETING AUTHORISATION HOLDER**

Brillpharma (Ireland) Limited
Inniscarra
Main Street
Rathcoole
Dublin
Ireland

**8 MARKETING AUTHORISATION NUMBER**

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 23rd November 2018
Date of last renewal: 22nd November 2023

## 10 DATE OF REVISION OF THE TEXT

August 2023