1 NAME OF THE MEDICINAL PRODUCT

Bendroflumethiazide 2.5mg Tablets

Bendroflumethiazide 5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Bendroflumethiazide 2.5mg
Each tablet contains Bendroflumethiazide 5mg

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets.

White to off white circular, biconvex, uncoated tablets.

White to off white, circular, flat, beveled edged, uncoated tablets with '5' debossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bendroflumethiazide is indicated for:

1. Cases where the reduction of fluid retention by diuresis is required, oedema of cardiac, renal or hepatic origin and iatrogenic oedema
2. Bendroflumethiazide produces a moderate but usefully prolonged fall of blood pressure in hypertensive patients. It may be used as the sole antihypertensive agent, or, as an adjunct to other drugs whose action it potentiates. In non-oedematous patients, there may be little noticeable diuretic effect.

4.2 Posology and method of administration

For oral administration

It is recommended that the tablets should be taken in the morning to avoid nocturia.

Adults and children aged 12 years and over:

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 – 5mg taken in the morning. Higher doses are rarely necessary. When Bendroflumethiazide is used concurrently with other specific hypotensive agents, the dosage of such agents should be reduced and then adjusted as necessary.

Children under 12 years of age: Dosage in children may be up to 400 mcg/kg bodyweight initially, reducing to 50-100 mcg/kg bodyweight daily for maintenance. A more appropriate dosage form may be required.

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

4.3 Contraindications

- Sensitivity to bendroflumethiazide or other sulphonamide-derived drugs or to any of the excipients listed in section 6.1 .

- Severe renal insufficiency or anuria
- Severe hepatic impairment (risk of precipitation of encephalopathy)
- Addison's disease.
- Refractory Hyperkalemia, hyponatremia or hypercalcemia
- Symptomatic hyperuricemia

4.4 Special warnings and precautions for use

Hypokalaemia:
Electrolytes should be monitored during treatment as continued or intensive use of bendroflumethiazide may result in hypokalaemia. This effect may be enhanced with concomitant use of medicines that can also cause hypokalaemia such as other diuretics or beta-2 agonists. Hypokalaemia can increase the risk of cardiac arrhythmia particularly when the patient is also taking an anti-arrhythmic, anti-histamine, anti-malarial, anti-psychotic or digoxin (see section 4.5).

Potassium replacement or conservation may be necessary in patients at risk from the cardiac effects of hypokalaemia, such as those with prolonged QT intervals, severe heart disease, those taking digitalis preparations or high doses of diuretics and in patients with severe liver disease. If hypokalaemia (< 3.4 mmol potassium) is detected, it must be corrected and it should be prevented in at-risk patients.

Potassium supplements should not be given in renal insufficiency complicated by hyperkalaemia.

Potassium supplementation alone may not be sufficient to correct hypokalaemia in patients who are also deficient in magnesium.

Hyponatraemia:
Some patients may be particularly susceptible to hyponatraemia, including the elderly and those with severe heart failure who are very oedematous, particularly with large doses of thiazides in conjunction with restricted salt in the diet. The onset of hyponatraemia can be sudden and life-threatening.

All patients, including the elderly who may be particularly susceptible, should be carefully observed for signs of fluid and electrolyte imbalance, especially in the presence of vomiting or during parenteral fluid therapy.

Regular serum electrolyte determinations should be performed in the elderly and in patients receiving long-term therapy.

Hypomagnesaemia
There is an increased risk of hypomagnesaemia in patients with alcoholic cirrhosis taking bendroflumethiazide. Hypomagnesaemia has been implicated as a risk factor for arrhythmias. Electrolyte levels including magnesium should be monitored during treatment of patients with alcoholic cirrhosis.

Hypercalcaemia
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.

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.

Mild or moderate hepatic or renal impairment
Use with caution in renal impairment (severe renal insufficiency is a contraindication to use, see 4.3). Renal function should be monitored during bendroflumethiazide therapy. Thiazides can cause electrolyte imbalance which is more severe in patients with hepatic and renal impairment and in those receiving higher or prolonged doses.

Use with caution in hepatic impairment (severe hepatic impairment is a contraindication to use, see 4.3). In case of hepatic impairment, thiazide diuretics may precipitate hepatic encephalopathy, particularly in case of electrolyte imbalance. Administration of the diuretic must be stopped immediately if this occurs.

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

Concomitant use with lithium
Bendroflumethiazide inhibits the tubular elimination of lithium resulting in an elevated plasma lithium concentration and risk of toxicity. Both lithium and thiazide and related diuretics can cause hypokalaemia, increasing the risk of torsade de pointes. Avoid concurrent use unless lithium levels and potassium concentrations can be closely monitored and the lithium dose adjusted as necessary. Advise patients to report lithium adverse effects (tremor, dysarthria, ataxia, confusion) (see section 4.5).

Concomitant use with pimozide, sertindole or thioridazine
Diuretic-induced hypokalaemia increases the risk of ventricular arrhythmias with pimozide, sertindole and thioridazine therefore concomitant use should be avoided (see section 4.5).

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazides and thiazide-related diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Systemic lupus erythematosus
Thiazide diuretics can induce a cutaneous lupus-like adverse reaction. Thiazide diuretics may also exacerbate or activate systemic lupus erythematosus (SLE) in susceptible patients.

Pancreatitis
Pancreatitis has been reported during thiazide therapy. Thiazide therapy is associated with hypercalcaemia and hyperlipidaemia both of which are risk factors for pancreatitis.

Gout
Thiazide use may aggravate gout. Serum uric acid levels may be raised with or without gout in some patients.

Diabetes mellitus
Bendroflumethiazide may precipitate diabetes mellitus and may impair glycaemic control in patients with diabetes.

Hyperlipidaemia
Caution should be exercised when used in patients with hyperlipidaemia.

Important information regarding the ingredients of this medicine

Lactose:
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

Pharmacodynamic interactions

- **Alcohol**: Co-administration of alcohol may potentiate orthostatic hypotension.
- **Aldesleukin**: Enhanced hypotensive effect may occur when aldesleukin and thiazide diuretics are used concomitantly.
- **Anaesthetics, general**: Enhanced hypotensive effect may occur when general anaesthetics and thiazide diuretics are used concomitantly.
- **Antibacterials**: Severe hyponatraemia may occur with concomitant administration of bendroflumethiazide and trimethoprim.
- **Anti-depressants**: Co-administration of tricyclic antidepressants may increase the risk of postural hypotension. Enhanced hypotensive effect with monoamine oxidase inhibitors (MAOIs). Possibly increased risk of hypokalaemia if thiazides given with reboxetine.
- **Antidiabetics**: Bendroflumethiazide can act synergistically with chlorpropamide to increase the risk of hyponatraemia
- **Anti-epileptics**: There is a risk of hyponatraemia occurring when thiazide diuretics, such as bendroflumethiazide, are used concomitantly with carbamazepine

- **Anti-fungals**: Increased risk of hypokalaemia with concurrent use of thiazide diuretics and amphotericin.

- **Antihypertensives**: Thiazide diuretics may enhance the effect of other hypotension producing medications, including angiotensin-converting enzyme (ACE) inhibitors (potential for enhanced first-dose hypotension), angiotensin-II antagonists, calcium channel blockers, beta-blockers, alpha-blockers (increased risk of first-dose hypotension with alpha-blockers such as prazosin), hydralazine and diazoxide. The dosage of concomitantly administered antihypertensive drugs may need to be reduced when bendroflumethiazide is added to the regimen

- **Calcium salts & Vitamins**: There is a risk of hypercalcaemia with calcium salts and vitamin D. There is an increased risk of developing milk-alkali syndrome in patients given large amounts of calcium or vitamin D in combination with thiazides.

- **Calcium-channel blockers and peripheral vasodilators**: The hypotensive effect of calcium channel blockers and moxisylyte may be enhanced when co-administered with bendroflumethiazide.

- **Corticosteroids**: Increased risk of thiazide-induced hypokalaemia, mainly with the naturally occurring corticosteroids such as cortisone and hydrocortisone. Adrenocorticotropic hormone (ACTH) can also exacerbate hypokalaemia associated with bendroflumethiazide use. Fluid retention associated with corticosteroid use may antagonise the diuretic/antihypertensive effect.

- **Diuretics**: Increased risk of hypokalaemia with concurrent administration of other thiazides and other diuretics including acetazolamide and loop diuretics.

- **Dopaminergics**: Enhanced hypotensive effect may occur when levodopa and thiazide diuretics are used concomitantly.

- **Hormone antagonists**: There is an increase risk of hypercalcaemia when thiazides are used concomitantly with toremifene. There is an increased risk of hyponatraemia when thiazides are used concomitantly with aminoglutethimide.

- **Nitrates**: Enhanced hypotensive effect may occur when nitrates and thiazide diuretics are used concomitantly.

- **Prostaglandins**: Hypotensive effect may be potentiated by alprostadil.

- **Theophylline**: Concomitant administration of xanthines such as theophylline and bendroflumethiazide increases the risk of hypokalaemia.

- **Sympathomimetics**: Increased risk of hypokalaemia with thiazide diuretics and high doses of beta$_2$ sympathomimetics.

- **Ulcer healing drugs**: Potential for severe hypokalaemia with carbenoxolone. Patients should be monitored and given potassium supplements when required.

- **Barbiturates**: Postural hypotension associated with therapy may be enhanced by concomitant ingestion of barbiturates.

- **Opioids**: Postural hypotension associated with therapy may be enhanced by concomitant ingestion of opioids.

Pharmacokinetic interactions

- **Anion exchange resins**: Colestipol and colestyramine reduce absorption of thiazides. This can be prevented by leaving an interval of two hours between doses of bendroflumethiazide and the anion exchange resin.

Effect of other medicinal products on bendroflumethiazide

- **Analgesics**: Non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin or ketorolac antagonise the diuretic effect of bendroflumethiazide. This occurs to a lesser extent with ibuprofen, piroxicam and naproxen. The effects of concurrent use should be monitored and the dose of bendroflumethiazide modified if necessary.

- **Oestrogens and progestogens**: Oestrogens and combined oral contraceptives antagonise the diuretic effect of thiazides.

Effect of bendroflumethiazide on other medicinal products

- **General**: Some electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia) may increase the toxicity of certain other drugs (e.g. digitalis preparations and drugs inducing QT interval prolongation syndrome).

- **Analgesics:** Diuretics may increase the risk of nephrotoxicity of non-steroidal anti-inflammatory drugs (NSAIDs). The effects of concurrent use should be monitored and the dose of bendroflumethiazide modified if necessary.

- **Anti-arrhythmics (see section 4.4):** The cardio toxicity of disopyramide, amiodarone, flecainide and quinidine is increased if hypokalaemia occurs. Action of lidocaine and mexiletine is antagonised by hypokalaemia. Hypokalaemia increases risk of ventricular arrhythmias with sotalol, a beta-blocker.

- **Antidiabetics:** Bendroflumethiazide may antagonise the hypoglycaemic effects of antidiabetic drugs including insulin possibly necessitating adjustment of the dose of the antidiabetic agent.

- **Antigout agents:** Potential for increased toxicity and hypersensitivity/allergic reactions with concomitant use of allopurinol and thiazide diuretics.

- **Antihistamines (see section 4.4)**: Bendroflumethiazide-induced hypokalaemia may increase the risk of arrhythmias with drugs that prolong the QT interval, such as astemizole and terfenadine.

- **Antihypertensives**: Concurrent administration of thiazides with beta-blockers or diazoxide has the potential to produce hyperglycaemia which may necessitate adjustment of the dose of antidiabetic medication including insulin. Intravascular immune haemolysis may occur in patients taking bendroflumethiazide and methyldopa.

- **Antimalarials** (see section 4.4): Bendroflumethiazide -induced hypokalaemia may increase the risk of arrhythmias with drugs that prolong the QT interval, such as halofantrine.

- **Antipsychotics (see section 4.4)**: Diuretic-induced Hypokalaemia increases the risk of ventricular arrhythmias with pimozide or sertindole and thioridazine therefore concomitant use should be avoided. Enhanced hypotensive effect may occur when phenothiazines and thiazide diuretics are used concomitantly.

- **Ciclosporin**: Increased risk of nephrotoxicity and/or hypermagnesaemia with concomitant use of ciclosporin and thiazide diuretics, such as bendroflumethiazide.

- **Cytotoxics**: Concomitant use with cisplatin can lead to an increased risk of nephrotoxicity and ototoxicity.

- **Digoxin (see section 4.4)**: 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, treatment with cardiac glycosides may have to be temporarily suspended and a potassium supplement given to restore stability.

- **Lithium (see section 4.4)**: Bendroflumethiazide inhibits the tubular elimination of lithium resulting in an elevated plasma lithium concentration and risk of toxicity. Both lithium and thiazide and related diuretics can cause hypokalaemia, increasing the risk of torsade de pointes. Avoid concurrent use unless lithium levels and potassium concentrations can be closely monitored and the lithium dose adjust as necessary. Advice patients to report lithium adverse effects (tremor, dysarthria, ataxia, confusion).

- **Muscle relaxants**: Diuretic-induced hypokalaemia may potentiate the neuromuscular blocking activity of non-depolarising muscle relaxants, such as tubocurarine, gallamine, alcuronium and pancuronium. An enhanced hypotensive effect may occur with tizanidine.

- **Interference with tests for parathyroid function:** Because thiazides may affect calcium metabolism, bendroflumethiazide may interfere with tests for parathyroid function. Bendroflumethiazide should be stopped before parathyroid function is tested.

4.6 Fertility, pregnancy and lactation

Diuretics are best avoided for the management of oedema of pregnancy or hypertension in pregnancy as their use may be associated with hypokalemia, increased blood viscosity and reduced placental perfusion.
There is inadequate evidence of safety in human pregnancy and foetal bone marrow depression and thrombocytopenia has been described. Foetal and neonatal jaundice have also been described
Bendroflumethiazide is secreted in mother's milk; therefore, breast feeding should be avoided. Treatment with large doses of thiazides may suppress lactation.

4.7 Effects on ability to drive and use machines

Dizziness, drowsiness, postural hypotension and mental confusion may occur. This may impair ability to drive or operate machinery

4.8 Undesirable effects

Summary of safety profile
The safety profile of bendroflumethiazide includes a degree of electrolyte imbalance. Serious adverse reactions include pancreatitis, hypersensitivity reactions, serious skin reactions and blood dyscrasias.

Adverse reactions listed below are based on available data for bendroflumethiazide and classified according to frequency and system organ class (SOC). Frequency categories are defined according to 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), and not known (cannot be estimated from the available data).

Table 1. Adverse reactions

System	Very	Common	Uncommo	Rare	Very	Not known

organ class	common		n		rare	
Blood and lymphatic system disorders				Blood dyscrasias including neutropenia, agranulocytosis, aplastic anaemia, thrombocytopenia and leucopenia		
Immune system disorders						Hypersensitivity reactions
Endocrine disorders						Thiazides may cause hyperglycaemia and aggravate or unmask diabetes mellitus.
Nervous system disorders						Headache Dizziness Paraesthesia Drowsiness
Eye disorders						Choroidal effusion [a]
Vascular disorders						Postural hypotension Vasculitis
Respiratory, thoracic and mediastinal disorders						Pneumonitis and pulmonary oedema (as part of hypersensitivity reaction)
Gastrointestinal disorders				Pancreatitis		Nausea Vomiting Diarrhoea Constipation Gastric irritation Dry mouth Thirst
Hepatobiliary disorders						Cholecystitis Cholestasis
Skin and subcutane						Rashes (including

ous tissue disorder						exfoliative dermatitis) Photosensitivity Skin eruptions resembling lichen planus and subacute cutaneous lupus erythematosus Erythema multiforme Pseudoporphyria
Musculoskeletal and connective tissue disorders						Systemic lupus erythematosus
Renal and urinary disorders						Acute interstitial nephritis Non-opaque urate calculi Oliguria
Reproductive system and breast disorders						Impotence (reversible on discontinuing the drug)
Investigations						Increased triglyceride, total cholesterol, low-density and very-low density lipoprotein cholesterol concentrations Hypokalaemia Hypomagnesaemia Hyponatraemia Hypercalcaemia Hypochloraemic alkalosis Hyperuricaemia with/ without gout

[a] see subsection below for additional information

Description of selected adverse reactions
Choroidal effusion
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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs and Symptoms
Symptoms of overdosage include anorexia, nausea, vomiting, diarrhoea, dehydration, hypotension, dizziness, weakness, muscle cramps, convulsions, increased frequency of micturition with polyuria and thirst, paraesthesia, and tetany.

Extreme cases may show depletion of intravascular volume, hypotension and peripheral circulatory failure.

Hypokalaemia can occur and is especially important in patients with pre-existing cardiac disease. Hyponatraemia, hypomagnesaemia, hypercalcaemia, hypo- or hyperglycaemia and metabolic alkalosis are also possible. Electrolyte abnormalities can lead to arrhythmias.

CNS depression (*e.g.* drowsiness, lethargy and coma) may occur without cardiovascular or respiratory depression.

Management of overdose*:*

Treatment should be supportive and directed at fluid and electrolyte replacement which should be monitored together with the blood pressure, blood glucose, ECGs and renal function. Cathartics should be avoided.

There is no specific antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diuretic, ATC code: C03AA01

Bendroflumethiazide is a thiazide diuretic and reduces the reabsorption of electrolytes from renal tubules thereby increasing the excretion of sodium and chloride and subsequently 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

There are no pre-clinical data of relevance to the prescriber which are additional to those included in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous Lactose

Talc

Pregelatinised starch

Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/PVDC Aluminium foil blisters: 3years
HDPE containers: 18 months

6.4 Special precautions for storage

PVC/PVDC Aluminium foil blisters: Do not store above 25ºC. Store in the original package

HDPE containers: Do not store above 25ºC. Keep the container tightly closed.

6.5 Nature and contents of container

PVC/PVDC Aluminium foil blister, pack sizes of 14, 28, 56, 84 tablets.

HDPE tablet containers, pack sizes of 50, 100, 250, 500, 1000 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0082
PL 17907/0083

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/09/2011

10 DATE OF REVISION OF THE TEXT

22/01/2026