SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bendroflumethiazide 2.5mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bendroflumethiazide 2.5 mg per tablet.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Bendroflumethiazide 2.5 mg tablets are presented as white flat bevelled edge tablets engraved with the company logo on one side and A268 on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Oedema:

Bendroflumethiazide is indicated in the treatment of oedema associated with conditions such as congestive heart failure, nephrotic syndrome, cirrhosis of the liver.

Essential hypertension:

Bendroflumethiazide may be used as the sole antihypertensive agent or used concurrently with other specific hypotensive agents whose action it potentiates.

4.2. Posology and method of administration

Route of administration: Oral

ADULTS:

Oedema:
5.0 - 10.0 mg once daily or on alternate days

Maintenance:
2.5 - 5.0 mg two or three times a week

Essential hypertension:
2.5 mg in the morning, alone or in conjunction with other antihypertensive agents in more severe hypertension.

The dosage should be reduced in the elderly with impaired renal function.

CHILDREN:

Diuretic - Initial: 0.4 mg per kg of body-weight per day.

Maintenance: 0.05 to 0.1 mg per kg of body-weight per day.

Antihypertensive: 0.05 to 0.4 mg/kg body-weight per day as a single dose or in two divided daily doses, adjusted according to response.

4.3 Contraindications

Bendroflumethiazide is contra-indicated in patients hypersensitive to this drug or any of the excipients and in patients with severe renal insufficiency, Addison's disease, refractory hypokalaemia, hyponatraemia, hypercalcaemia, serious hepatic disorders and symptomatic hyperuricaemia.

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 balance 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.

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.

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

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 increased 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.

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

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.

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 and 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 cardiotoxicity 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, 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 adjusted as necessary. Advise patients to report lithium adverse effects (tremor, dysarthria, ataxia, confusion).
Muscle relaxants
Diuretic-induced hypokalaemia may enhance 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. 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 hypovolaemia, increased blood viscosity and reduced placental perfusion.

There is inadequate evidence of safety in human pregnancy and some workers have described foetal bone marrow depression and blood disorders including neutropenia and thrombocytopenia. When given in late pregnancy, neonatal thrombocytopenia has been reported. Foetal and neonatal jaundice have also been described.

As diuretics pass into breast milk, they should be avoided in mothers who wish to breast-feed.

Bendroflumethiazide may suppress lactation.

4.7. Effects on ability to drive and use machines

None reported.

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).

System organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders				Blood dyscrasias, including neutropenia, agranulocytosis, aplastic anaemia, thrombocytopenia and leucopenia		
Immune system disorders						Hypersensitivity reactions
Endocrine disorders						Thiazides ma cause hyperglycaemia and aggravate unmask diabet mellitus.

Nervous system disorders						Headache Dizziness Paraesthesia Drowsiness
Eye disorders						Choroidal effusio[a]
Vascular disorders						Postural hypotension Vasculitis
Respiratory, thoracic and mediastinal disorders						Pneumonitis and pulmonary oedema (as part hypersensitivity reaction)
Gastrointestinal disorders				Pancreatitis		Nausea Vomiting Diarrhoea Constipation Gastric irritation Dry Mouth Thirst
Hepatobiliary disorders						Cholestasis Cholecystitis
Skin and subcutaneous tissue disorders						Rashes (including exfoliative dermatitis) Photosensitivity Skin eruption resembling liche planus ar subacute cutaneous lupu erythematosus Erythema multiforme Pseudoporphyria
Musculoskeletal and connective tissue disorders						Systemic lupu erythematosus
Renal and urinary disorders						Acute interstiti nephritis Non-opaque ura calculi Oliguria
Reproductive						Impotence

system and breast disorders						(reversible d discontinuing th drug)
Investigations						Increased triglyceride, tot cholesterol, lov density and very low density lipoprotein cholesterol concentrations Hypokalaemia. Hypomagnesaem Hyponatraemia Hypercalcaemia Hypochloraemic alkalosis Hyperuricaemia with/without gou

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 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 classification : Low-Ceiling Diuretics Thiazides - Bendroflumethiazide
ATC code : C03A A01

Bendroflumethiazide is a thiazide diuretic which reduces the reabsorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium and chloride ions, and consequently of water. Thiazides also reduce the carbonic anhydrase activity so that bicarbonate excretion is increased but this inhibitory action is weak as compared with the effect on chloride excretion and does not appreciably alter the pH of the urine. In response to the increased tubule load of sodium, the rate of tubular secretion of potassium and exchange with sodium is augmented and an increased amount of potassium is lost in the urine.

Diuresis is initiated after about 2 hours of bendroflumethiazide administration, the maximum diuresis occurs within 12 hours and a significant diuretic effect persists for 24 hours. In subjects with normal renal function; sodium and chloride output is increased twofold after 5 mg of bendroflumethiazide, 7.5 mg increases sodium output threefold and chloride output fourfold. 10 mg does not increase sodium and chloride output significantly more than 7.5 mg i.e. the dose response curve becomes flat. Potassium excretion is doubled after 5 mg of bendroflumethiazide, in normal subjects doubling this dose has no effect on potassium excretion.

Bendroflumethiazide has, like other thiazides, a lowering effect on blood pressure which is considered to be due to sodium depletion; and it also enhances the effects of other antihypertensive agents.

Bendroflumethiazide is used in oedema associated with congestive heart failure, renal and hepatic disorders.

In the treatment of oedema, the usual initial dose is 5 mg daily, reduced to a dose of 2.5 mg daily or 5 mg on alternative days. A suggested initial dose for children is up to
400 micrograms per kg body weight daily, reduced to 50 - 100 micrograms per kg for maintenance.

In the treatment for hypertension the usual dose is 2.5 mg to 10 mg daily either alone, or in conjunction with other antihypertensive agents.

5.2. Pharmacokinetic properties

Bendroflumethiazide is more completely absorbed from the gastro-intestinal tract than chlorothiazide, reflecting its greater lipid solubility. Maximum diuresis occurs within 12 hours of bendroflumethiazide administration, although a significant diuretic effect persists for 24 hours.

Bendroflumethiazide is fairly extensively metabolised: about 30% is excreted unchanged in the urine. It is estimated to have plasma half-life of about 3 or 4 hours.

5.3. Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose
Maize starch
Pregelatinised maize starch
Magnesium stearate
Starch 1500
Potable water

6.2. Incompatibilities

Bendroflumethiazide preparations should not be administered concurrently with lithium carbonate.

6.3. Shelf life

As packaged for sale:
3 years for opaque plastic containers.
2 years for blister packaging.

6.4. Special precautions for storage

Blister Packs: Do not store above 25°C, store in original package.
Plastic Containers: Do not store above 25°C, keep container tightly closed.

6.5. Nature and contents of container

Bendroflumethiazide tablets are packed in the following containers and closures.

1.	Opaque plastic containers composed of polypropylene tubes and polyethylene-made tamper-evident closures for pack sizes of 28, 30, 42, 50, 56, 60, 84, 90, 100, 112, 250, 500 and 1000 tablets.
2.	Opaque plastic containers composed of either high density polypropylene or high density polyethylene with a tamper-evident or child-resistant tamper-evident closure composed of high density polyethylene with a packing inclusion of standard polyether foam or polyethylene or polypropylene made filler in pack sizes of 28, 30, 42, 50, 56, 60, 84, 90, 100, 112, 250, 500 and 1000 tablets.
3.	Blister packs of aluminium/opaque PVC. It is subsequently packed in printed boxboard cartons in pack sizes of 28, 30, 42, 56, 60, 84, 90 and 112 tablets.

Not all pack sizes may be marketed.

6.6. Instructions for Use, Handling and Disposal

No special instructions for use/handling.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Frimley Business Park,

Frimley,
Camberley,
Surrey,
GU16 7SR,
United Kingdom.

8. MARKETING AUTHORISATION NUMBER

PL 04416 / 0529

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/06/2006

10 DATE OF REVISION OF THE TEXT

26/11/2020