SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bendroflumethiazide 5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Bendroflumethiazide 5mg.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets for oral use.
White, circular flat faced tablets with bevelled edges, B 5 separated by a break line on one face and plain on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bendroflumethiazide is a diuretic. The tablets are indicated for the treatment of essential hypertension and oedema associated with such conditions as nephrotic syndrome, cirrhosis of the liver, congestive heart failure and pre-menstrual oedema.

4.2 Posology and method of administration

Adults:

Oedema	5-10mg daily in the morning initially. Maintenance: usually 2.5mg-5mg on only two or three days in the week. A single dose may be sufficient
Essential Hypertension	2.5mg in the morning. Doses above 2.5mg are rarely necessary.
Pre-menstrual syndrome	2.5mg each morning for seven days before the period is due.

Children:

Oedema	Up to 400 micrograms per kg body weight daily initially, reducing to 50-100 micrograms per kg 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."

4.3 Contraindications

Bendroflumethiazide tablets are contraindicated in patients with known hypersensitivity to thiazides; hypercalcaemia, hyponatraemia, refractory hypokalemia, severe renal and hepatic insufficiency, symptomatic hyperuricaemia and Addison's disease.

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.

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 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.

4.7 Effects on ability to drive and use machines

None stated.

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 organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders				Blood dyscrasias, including neutropenia, agranulocytosis, aplastic anaemia,		
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						Pneumonitis and pulmonary oedema (as part of

disorders						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 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 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: Low-Ceiling Diuretics,thiazides-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

Bendroflumethiazide may be completely absorbed from the gastrointestinal tract and it is fairly extensively metabolised. About 30% is excreted unchanged in the urine. The onset of diuretic action of the thiazides following oral administration occurs within two hours and the peak effect between three and six hours after administration. The duration of the diuretic action of bendroflumethiazide is between 18 and 24 hours. The onset of the hypotensive action is generally three or four days.

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

Lactose monohydrate

Pregelatinised maize starch
Maize Starch
Purified talc
Magnesium stearate

6.2 Incompatibilities

None known

6.3 Shelf life

36 months in amber glass bottles.
36 months in polyethylene/polypropylene containers.
36 months in PVC/aluminium foil blister packs.

6.4 Special precautions for storage

Do not store above 25°C.Store in the original package. Keep the containers tightly closed.

6.5 Nature and contents of container

Amber glass bottles with a plastic cap containing 50 tablets.
Polypropylene or polyethylene containers containing 100, 250, 500, 1000 and bulk amount of tablets.
Blister packs of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or 14, 28, 56, 84, 112 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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PL 36722/0033

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