SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Bendroflumethiazide Tablets 5.0 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Bendroflumethiazide 5.0 mg per tablet
For excipients, see 6.1.

3 PHARMACEUTICAL FORM
Tablet.
White flat bevelled edge tablets engraved with the company logo on one side and A269 on the other.

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:
Initially: 5 - 10mg in the morning, once daily or on alternative days.

Maintenance: 2.5 - 5mg two or three times a week.

Essential hypertension: 2.5 mg in the morning, alone or in conjunction with 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.

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

Hypersensitivity to Bendroflumethiazide or any of the excipients.

Bendroflumethiazide is contra-indicated in patients with:

- severe renal insufficiency
- Addison's disease
- refractory hypokalaemia
- hyponatraemia
- hypercalcaemia
- serious hepatic disorders
- symptomatic hyperuricaemia.

4.4 Special warnings and precautions for use

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 produce a degree of electrolyte imbalance, especially in patients with renal or hepatic impairment or when dosage is high or prolonged. 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 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.

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

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

**Analgesics:** Diuretics such as bendroflumethiazide increase the risk of nephrotoxicity associated with non-steroidal anti-inflammatory analgesics (NSAIDs). NSAIDs, particularly indometacin and ketorolac may antagonise the natriuresis and increase in plasma renin activity caused by thiazide diuretics. It may also reduce the antihypertensive effect and increase in urine volume caused by thiazide diuretics, possibly by inhibiting renal prostaglandin synthesis and/or by causing sodium and fluid retention. Concomitant use with opiates leads to an increased risk of postural hypotension.

**Anion-exchange resins:** colestyramine and colestipol lead to decreased absorption of thiazides. It has been recommended that administration is at least 2 hours prior to, or after the ingestion of bendroflumethiazide.

**Antidiabetics:** Concurrent administration of bendroflumethiazide in patients receiving sulphonylureas may impair control of diabetes by antagonising the hypoglycaemic effect.

**Chlorpropamide** increases the risk of hyponatraemia associated with taking thiazides such as bendroflumethiazide in combination with potassium-sparing diuretics.

**Antiepileptics:** There is an increased risk of hyponatraemia with carbamazepine.

**Antifungals:** There is an increased risk of hypokalaemia if thiazides are given with amphotericin.

**Antihistamines:** Patients with hypokalaemia or other electrolyte imbalance have an increased risk of ventricular arrhythmias with terfenadine.

**Antihypertensives:** Concurrent use of bendroflumethiazide with antihypertensives enhances the hypotensive effect. There is an increased risk of first-dose hypotensive effect of post-synaptic alpha-blockers such as prazosin.
Antipsychotics: Patients with hypokalaemia have an increased risk of ventricular arrhythmias with pimozide. Concomitant use should be avoided.

Alprostadil: Concomitant use with alprostadil enhances the hypotensive effect.

Anti-arrhythmics: The cardiac toxicity associated with amiodarone, disopyramide, flecainide, and quinidine is increased if hypokalaemia occurs. The action of lidocaine and mexiletine is antagonised by hypokalaemia.

Antidepressants: There is a possible increased risk of postural hypotension with tricyclic antidepressants and of hypokalaemia if thiazides are given with reboxetine.

Beta-blockers: Use with bendroflumethiazide enhances the hypotensive effect. Patients with hypokalaemia have an increased risk of ventricular arrhythmias with sotalol.

Calcium salts: There is an increased risk of hypercalcaemia with thiazides such as bendroflumethiazide.

Calcium-channel blockers: Concomitant use with bendroflumethiazide enhances the hypotensive effect.

Cardiac glycosides: The concurrent use of cardiac glycosides with thiazide diuretics may enhance the possibility of cardiac toxicity associated with hypokalaemia, resulting in cardiac arrhythmias.

Corticosteroids: Xanthines, beta-agonists, ACTH There is an increased risk of hypokalaemia with thiazides such as bendroflumethiazide and the diuretic effect is antagonised.

Cytotoxics: Concurrent use of diuretics such as bendroflumethiazide with cisplatin increases the risk of nephrotoxicity and ototoxicity.

Hormone Antagonists: There is an increased risk of hyponatraemia with aminoglutethimide.

Thiazides such as bendroflumethiazide increase the risk of hypercalcaemia with toremifene.

Moxislyte: Concomitant use with bendroflumethiazide enhances the hypotensive effect.

Muscle relaxants: An enhanced hypotensive effect is associated with concomitant use with baclofen and tizanidine. Bendroflumethiazide interacts with nondepolarising neuromuscular blocking drugs leading to prolonged neuromuscular blockade e.g. tubocurarine.

Oestrogens and Progestogens: The diuretic effect is antagonised with oestrogens and combined oral contraceptives.

Other diuretics: There is an increased risk of hypokalaemia if thiazides such as bendroflumethiazide, loop diuretics or acetazolamide are taken together.

Sympathomimetics: There is an increased risk of hypokalaemia if thiazides are given with high doses of bambuterol, fenoterol, formoterol, reproterol,
ritodrine, salbutamol, salmeterol, terbutaline and tulobuterol. Potentially serious hypokalaemia may result from beta2 agonist therapy.

Theophylline: There is an increased risk of hypokalaemia with thiazides such as bendroflumethiazide.

Ulcer-healing Drugs: There is an increased risk of hypokalaemia if thiazides are given with carbenoxolone. Carbenoxolone also antagonises the diuretic effect.

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

Other interactions, vitamin D preparations (leading to increased risk of hypercalcaemia), alcohol and barbiturates (leading to increased risk of postural hypotension) have also been reported.

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 hypovolaemia, increased blood viscosity and reduced placental perfusion.

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

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**

All thiazide diuretics can produce a degree of electrolyte imbalance, e.g. hypokalaemia.

Thiazide diuretics may raise the serum uric acid levels with subsequent exacerbation of gout in susceptible subjects.

Thiazide diuretics sometimes lower carbohydrate tolerance and the insulin dosage of the diabetic patient may require adjustment. Care is necessary when bendroflumethiazide is administered to those with a known predisposition to diabetes.

Postural hypotension, mild gastro-intestinal effects and diarrhoea; hypokalaemia, hypomagnesaemia, hyponatraemia, hypercalcaemia, hypochloraemic alkalosis, hyperuricaemia, gout, hyperglycaemia, and altered plasma lipid concentration.
Less commonly, rashes, photosensitivity; blood disorders (including neutropenia and thrombocytopenia – when given in late pregnancy neonatal thrombocytopenia has been reported); pancreatitis, intrahepatic cholestasis, and hypersensitivity reactions (including pneumonitis, pulmonary oedema, severe skin reactions) also reported.

Rarely, blood dyscrasias, including agranulocytosis, aplastic anaemia, thrombocytopenia and leucopenia, and pancreatitis have been reported with long term therapy. Skin rashes and impotence (reversible on withdrawal of treatment) have occasionally been reported.

**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 at: www.mhra.gov.uk/yellowcard.

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 classification: Low-Ceiling Diuretics Thiazides - Bendroflumethiazide
ATC code: CO3A 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. The excretion of other electrolytes, notably potassium and magnesium, is also increased. The excretion of calcium is reduced. Thiazides also reduce the 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 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 is 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

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose
Maize starch
Pregelatinised starch
Magnesium stearate

6.2 Incompatibilities

Not applicable.

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

Do not store above 25°C.

6.5 Nature and contents of container
1. Opaque plastic containers composed of polypropylene tubes and polyethylene 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 polyether foam or polyethylene or polypropylene 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 subsequently packed in printed cartons in pack sizes of 28, 30, 42, 56, 60, 84, 90 and 112 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special instructions for use/handling.

7 MARKETING AUTHORISATION HOLDER
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