SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Bendroflumethiazide 5mg Tablets BP

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 breakline on one face and plain on the reverse.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Bendroflumethiazide is indicated for:

- Cases where the reduction of fluid retention by dieresis is required; oedema of cardiac, renal or hepatic origin and iatrogenic oedema

- Bendroflumethiazide produces a moderate but fully prolonged fall of blood pressure in hypersensitive patients. It may be used as the sole antihypersensitive agent, or, as an adjunct to other drugs whose action it potentiates. In non-oedematous patients, there may be little noticeable diuretic effect.

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

- Bendroflumethiazide may also be used to suppress lactation
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.

Posology

Adults and children aged 12 years and over:

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

Essential Hypertension: The usual dose is 2.5mg-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.

Suppression of lactation: 5mg in the morning and 5mg at midday for about five days

Pre-menstrual syndrome: 2.5mg each morning for seven days before the period is due.

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.

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

4.3 Contraindications
Bendroflumethiazide tablets are contraindicated in patients with known hypersensitivity to Bendroflumethiazide, other thiazides and other excipients in the tablets.

Bendroflumethiazide is also contraindicated in patients with the following conditions:

- Hypercalcaemia, hyponatraemia, or refractory hypokalaemia
- 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 produce a degree of electrolyte imbalance, which is more severe 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 mellitus and gout; increased risk of hypomagnesaemia in alcoholic cirrhosis.

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

- Caution is required when treating patients with porphyria.
- Patients taking pimozide or thioridazine. (see section 4.5)

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Digoxin: 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.

Lithium: Bendroflumethiazide inhibits the tubular elimination of lithium, resulting in an elevated plasma lithium concentrations and risk of toxicity. Plasma lithium concentrations must be monitored when these drugs are given concurrently.

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

Others: Xanthines, beta-agonists, ACTH, and acetazolamide may exacerbate the hypokalaemia associated with thiazide use.

Muscle relaxants: The hypotensive effect of Bendroflumethiazide may be increased by baclofen and tizanidine. Thiazide diuretics may enhance the neuromuscular
blocking effects of the non-depolarising muscle relaxants, e.g. tubocurarine, gallamine, alcuronium and pancuronium.

**Corticosteroids:** Corticosteroids may exacerbate hypokalaemia associated with Bendroflumethiazide and its diuretic activity may be antagonized.

**Alcohol, barbiturates and opioids:** Postural hypotension associated with therapy may be enhanced by concomitant ingestion of alcohol, barbiturates or opioids.

**Anti-epileptic:** Concomitant use of carbamazepine may increase the risk of hyponatraemia.

**Anti-fungal:** There is an increased risk of hyponatraemia if thiazides are given with amphotericin.

**Vitamins:** The risk of hypercalcemia is increased by the concomitant intake of calcium salts or vitamin D preparations.

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

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

**Hormone antagonists:** There is an increased risk of hyponatraemia when thiazides are used concomitantly with aminoglutethimide. Thiazides can cause an increased risk of hypercalcemia with toremifene.

**Anion exchange resins:** 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 peripheral vasodilators:** The hypotensive effect of calcium-channel blockers and moxisylyte may be enhanced when co-administered with Bendroflumethiazide.

**Anti-depressants:** 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) may also give an increased hypotensive effect.

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

**Antipsychotics:** Hypokalaemia increases the risk of ventricular arrhythmias with pimozide or thioridazine; therefore, concomitant use should be avoided.

**Terfenadine:** Hypokalaemia or other electrolyte imbalance also increases the risk of ventricular arrhythmias with terfenadine.

**Laboratory tests:** Bendroflumethiazide may interfere with a number of laboratory tests, including estimation of serum protein-bound iodine and tests of parathyroid function.
**Allopurinol:** Bendroflumethiazide may antagonise the action of allopurinol by causing retention of urate in the kidney. Caution is advised when using this combination.

**Antidiabetics:** Bendroflumethiazide antagonises the hypoglycaemic effect of sulfonylureas, with a potential loss of diabetic control.

**Antihypertensive:** Bendroflumethiazide may enhance the antihypertensive effect of ACE inhibitors and angiotensin-II antagonists. There is an increased risk of first dose hypotensive effect of post-synaptic alpha-blockers such as prazosin.

**Calcium salts:** Bendroflumethiazide reduces urinary excretion of calcium so there is an increase risk of hypercalcaemia when calcium salts are taken concurrently. Serum calcium levels should be monitored to ensure that they do not become excessive.

**Sympathomimetics:** Sympathomimetics can cause hypokalaemia. The risk of serious heart arrhythmias in asthmatic patients may be increased if Bendroflumethiazide is added to their medication.

**Theophylline:** Concomitant administration of theophylline and Bendroflumethiazide increases the risk of hypokalaemia.

**Ulcer healing drugs:** There is an increased risk of hypokalaemia and a decrease in diuretic activity when carbenoxolone and Bendroflumethiazide are taken together. Patients should be monitored and given potassium supplements when required.

### 4.6 Fertility, Pregnancy and lactation

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 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, although the amounts passing into breast milk are small, its use should be avoided in mother’s who wish to breast feed.

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

Although Bendroflumethiazide may not affect driving ability directly, adverse events such as hypotension, dizziness etc may impact this ability. Therefore, patients experiencing such adverse events should take care not to drive or operate machinery.
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.

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

**Immune system disorders:**
Hypersensitivity reactions

**Metabolism and nutrition disorders:**
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 (hyperglycaemia reported).
Bendroflumethiazide may raise the serum uric acid levels with subsequent exacerbation of gout in susceptible subjects (hyperuricaemia). Plasma lipids may be altered in patients taking Bendroflumethiazide.

**Cardiac and vascular disorders:**
Postural hypotension

**Gastrointestinal disorders:**
Mild gastro-intestinal effects, nausea, vomiting, diarrhoea, constipation and gastric irritation have all been reported.

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

**Hepatobiliary disorders:**
Pancreatitis, intrahepatic cholestasis

**Respiratory, thoracic and mediastinal disorders:**
Hypersensitivity reactions (including pneumonitis, pulmonary oedema,) also reported.

**Blood and lymphatic system disorders:**
Blood dyscrasias including agranulocytosis, aplastic anaemia, neutropenia, thrombocytopenia (neonatal thrombocytosis is reported when given in late pregnancy) and leucopenia, and pancreatitis have been reported with long term therapy may occur rarely.

**Reproductive system and breast disorders:**
Impotence (reversible on withdrawal of treatment)

**Skin and subcutaneous tissue disorders:**
Rash (including exfoliative dermatitis), photosensitivity, severe skin reactions may occur.

**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, increased frequency of micturition with polyuria and thirst, paraesthesia, tetany, gastrointestinal bleeding, hyponatraemia. Extreme cases may show depletion of intravascular volume, hypotension and peripheral circulatory failure. Mild hypo- or hyperglycaemia, hypokalaemia and metabolic alkalosis are likely to be present if diuresis is profound.

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

*Treatment:* Activated charcoal may help reduce absorption of substantial amounts if given within one hour of ingestion. Treatment should be symptomatic and directed at fluid and electrolyte replacement which should be monitored together with the blood pressure and renal function. In the case of recent ingestion gastric lavage should be conducted. Hyponatraemia should be treated with water deprivation rather than by the administration of sodium chloride. Cathartics should be avoided.

There is no specific antidote.

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### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties
Pharmacotherapeutic Group: Low-Ceiling Diuretics, thiazides-

ATC code: C03AA01

Bendroflumethiazide is a thiazide diuretic. The mechanism whereby the thiazides exert their antihypertensive effect has not been clearly established. Bendroflumethiazide reduces the reabsorption of electrolytes from renal tubules thereby increasing the excretion of sodium and chloride and subsequently of water. Sodium and chloride ions are excreted in equivalent
proportions. The excretion of other electrolytes, notably potassium and magnesium, is also increased. Because potassium excretion is promoted, metabolic alkalosis may occur secondary to hypokalaemia. There is no important effect upon carbonic anhydrase. Bendroflumethiazide exerts its diuretic effect in about 2 hours and this lasts for 12 to 18 hours or longer. 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. 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.

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

Metabolism: There is indication 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

Lactose monohydrate
Pregelatinised maize starch
Maize Starch
6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months in amber glass bottles.
36 months in polyethylene/polypropylene containers.
24 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 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
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Milpharm Limited
MARKETING AUTHORISATION NUMBER(S)
PL 16363/0503

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