SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bendroflumethiazide 2.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bendroflumethiazide 2.5 mg

Excipients with known effect

Each tablet also contains 40 mg of lactose. For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

White biconvex tablets of 5.5mm diameter, marked MP18 on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bendroflumethiazide is indicated for:

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

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

Posology

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 mg given orally once daily in the morning or on alternate days usually produces the desired effect, but this dose can be increased to 10 mg if required;

maintenance dose 2.5 -10 mg two or three times weekly.

Essential hypertension: 2.5-5 mg once daily in the morning. 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: Initially the dosage may be up to 400 micrograms/kg bodyweight daily, reducing to the maintenance dose of 50-100 micrograms/kg bodyweight daily. A more appropriate dosage form may be required.

Elderly:

Particular caution is needed in the elderly. Their dosage may need to be reduced, particularly when renal function is impaired, because of their susceptibility to electrolyte imbalance.

Method of administration:
Oral.

4.3 Contraindications

- Hypersensitivity to thiazides or to any of the excipients listed in section 6.1
- Severe renal or hepatic insufficiency.
- Addison's disease.
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia.

4.4 Special warnings and precautions for use

- Bendroflumethiazide may precipitate or aggravate diabetes mellitus and may impair control of diabetes in patients receiving sulphonylureas.
- Supplementary potassium is strongly recommended in patients receiving digitalis who require prolonged diuretic treatment.
- Thiazide diuretics should be used with caution in patients with mild or moderate hepatic or renal impairment (avoid if severe). 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. Patients on long term treatment and elderly patients need blood tests to monitor blood electrolyte

levels and blood dyscrasias. May cause hypokalaemia, which may be corrected by adding potassium supplements or a potassium-sparing drug to the regimen.

- Increased risk of hypomagnesaemia in alcoholic cirrhosis.
- May aggravate gout. Serum uric acid levels may be raised with or without gout in some patients.
- Treat with caution in porphyria.
- May aggravate systemic lupus erythematosus.
- Blood dyscrasias and pancreatitis have been reported. (see section 4.8)
- Expectant mothers who receive thiazide diuretics may be at increased risk from acute haemorrhagic pancreatitis; thrombocytopenia has been reported in newborn infants following antepartum use of thiazides. (see section 4.6)
- Patients taking pimozide or thioridazine. (see section 4.5)
- 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.
- **Bendroflumethiazide tablets 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

- *Allopurinol:* Bendroflumethiazide may antagonise the action of allopurinol by causing retention of urate in the kidney. Caution is advised when using this combination.
- *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.
- *Corticosteroids:* Corticosteroids, ACTH, may exacerbate hypokalaemia associated with bendroflumethiazide and its diuretic activity may be antagonised.
- *Acetazolamide:* increased risk of hypokalaemia when thiazides and related diuretics given with acetazolamide.
- *Antifungals:* The risk of hypokalaemia is increased when amphotericin and bendroflumethiazide are taken concurrently.
- *Antidepressants:* There is an increased risk of postural hypotension if bendroflumethiazide is given with tricyclic antidepressants. There may also be a risk of hypokalaemia if thiazides are given with reboxetine.

Concomitant use with MAOIs may result in an enhanced hypotensive effect.

- *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.
- *Antiarrhythmics:* The cardiotoxicity of disopyramide, flecainide, amiodarone, and quinidine is increased if hypokalaemia occurs following the administration of bendroflumethiazide. The actions of lidocaine and mexiletine are antagonised by hypokalaemia.
- *Antipsychotics:* Hypokalaemia increases the risk of ventricular arrhythmias with sertindole, pimozide and thioridazine, so concomitant use should be avoided.
- *Digoxin:* The hypokalaemic effect of bendroflumethiazide may enhance sensitivity to digoxin when taken concurrently. Patients should be monitored for signs of digoxin intoxication, especially arrhythmias. The dose of digoxin should be reduced and potassium supplements given, should digoxin toxicity develop.
- *Lithium:* Bendroflumethiazide inhibits the tubular elimination of lithium, resulting in an elevated plasma lithium concentration and risk of toxicity. Plasma lithium concentrations must be monitored when these drugs are given concurrently.
- *Hormone antagonists:* There is an increased risk of hyponatraemia when bendroflumethiazide is used concomitantly with, aminoglutethamide. Bendroflumethiazide can cause an increased risk of hypercalcaemia when co-administered with toremifene.
- *Antiepileptics:* There is an increased risk of hyponatraemia when bendroflumethiazide and carbamazepine are taken concurrently.
- *Vitamins:* The risk of hypercalcaemia is increased if bendroflumethiazide is given with vitamin D.
- *Calcium salts:* Bendroflumethiazide reduces urinary excretion of calcium so there is an increased risk of hypercalcaemia when calcium salts are taken concurrently. Serum calcium levels should be monitored to ensure that they do not become excessive.
- *NSAIDs:* Bendroflumethiazide may enhance the 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.
- *Oestrogens and progestogens:* Oestrogens and combined oral contraceptives antagonise the diuretic effect of bendroflumethiazide.
- *Antidiabetics:* Bendroflumethiazide antagonises the hypoglycaemic effects of sulfonylureas (chlorpropamide), with a potential loss of diabetic control.
- *Muscle relaxants:* The hypotensive activity of bendroflumethiazide may be increased by baclofen and tizanidine. Bendroflumethiazide may enhance the neuromuscular blocking activity of non-depolarising muscle relaxants, such as tubocurarine, gallamine, alcuronium and pancuronium.

- *Antihypertensives:* Bendroflumethiazide may enhance the antihypertensive effect of ACE inhibitors, α and β- blockers, angiotensin-II antagonists and alprostadil. There is an increased risk of first dose hypotension if prazosin is given to a patient taking bendroflumethiazide.
- *Calcium channel blockers and peripheral vasodilators:* The hypotensive effect of, calcium channel blockers and moxisylyte may be enhanced when co-administered with bendroflumethiazide.
- *Nitrates:* enhanced hypotension effect when diuretics given with nitrates.
- *Cytotoxics:* Concomitant use with cisplatin can lead to an increased risk of nephrotoxicity and ototoxicity. Enhanced hypotensive effect when diuretics given with aldesleukin.
- *Levodopa:* enhanced hypotension effect when diuretics given with levodopa.
- *Alcohol:* enhanced hypotension effect when diuretics given with alcohol.
- *Anion exchange resins:* Colestyramine and colestipol reduce absorption of bendroflumethiazide. This can be prevented by leaving an interval of two hours between doses of bendroflumethiazide and the anion exchange resin.

4.6 Fertility, pregnancy and lactation

Bendroflumethiazide is best avoided for the management of oedema of pregnancy or hypertension in pregnancy as it crosses the placenta and their use may be associated with hypokalaemia, increased blood viscosity and reduced placental perfusion.

There is inadequate evidence of safety in human pregnancy. Foetal bone marrow depression and thrombocytopenia as well as neonatal jaundice have been reported.

Bendroflumethiazide suppresses lactation and although the amounts passing into breast milk are small, it should be avoided in mothers who wish to breast feed.

4.7 Effects on ability to drive and use machines

As bendroflumethiazide can cause dizziness, patients should make sure they are not affected before driving or operating machinery.

4.8 Undesirable effects

The following undesirable effects have been divided into the following categories: 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, Not known (cannot be estimated from the available data)

Effects on blood

Rare: Rarely, blood dyscrasias, including agranulocytosis, aplastic anaemia, thrombocytopenia and leucopenia, have been reported.

Hypersensitivity reactions

Not known: Rashes (including exfoliative dermatitis), photosensitivity, pneumonitis and pulmonary oedema have been reported occasionally.

Metabolic effects

Not known: Bendroflumethiazide may lower carbohydrate tolerance and the insulin dosage of some diabetic patients may require adjustment. Care is required when bendroflumethiazide is administered to patients with a known predisposition to diabetes. Bendroflumethiazide may raise serum uric acid levels and exacerbate gout in susceptible individuals. Plasma lipids may be altered in patients taking bendroflumethiazide.

Effects on electrolytes
Not known: Bendroflumethiazide administration may cause hypokalaemia, hyponatraemia, hypomangnesaemia, hypercalcaemia and hypochloraemic alkalosis Hypokalaemia may result in polyuria, malaise, muscle weakness or cramp, dizziness, nausea, anorexia or vomiting.

Gastrointestinal effects

Not known: Nausea, vomiting, diarrhoea, constipation and gastric irritation have all been reported.

Other reactions

Not known: Pancreatitis, intrahepatic cholestasis and impotence (reversible on withdrawal of treatment) have been reported. Postural hypotension or dizziness may also occur.

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 Google play or Apple App Store.

4.9 Overdose

*Symptoms***:** Nausea, vomiting, diarrhoea, dehydration, dizziness, weakness, muscle cramps, diuresis, increased frequency of micturition with polyuria and thirst. Extreme cases may show depletion of intravascular volume, hypotension and peripheral circulatory failure. Hypokalaemia and mild hypoglycaemia 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. Hyponatraemia should be treated with water deprivation rather than by the administration of sodium chloride. Cathartics should be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Thiazide diuretics ATC CODE; C03A A01

Mechanism of action

The mechanism whereby the thiazides exert their antihypertensive effect has not been clearly established.

Bendroflumethiazide inhibits the renal tubular absorption of salt and water by its action at the beginning of the distal convoluted tubule. Sodium and chloride ions are excreted in equivalent proportions. 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.

5.2 Pharmacokinetic properties

Absorption: Bendroflumethiazide has been reported to be completely absorbed from the gastrointestinal tract. Diuresis is initiated in about 2 hours and lasts for 12-18 hours or longer.

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

No relevant information to that contained elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Pregelatinised maize starch
Sodium starch glycollate
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Tablet containers: 3 years
Blister packs: 2 years

6.4 Special precautions for storage

Tablet containers: Do not store above 25°C. Store in the original container and keep the container tightly closed.

Blister packs: Do not store above 25°C. Store in the original package and keep container in the outer carton.

6.5 Nature and contents of container

Tablet Containers: High density polystyrene with polythene lids and/or polyproylene containers with polypropylene or polythene lids and polyurethane or polythene inserts.

Blister packs: 250 µm glass clear PVC and 20 µm aluminium foil coated with heat resistant print primer on one side and heat-seal lacquer on the other

Pack sizes: 28, 30, 50, 56, 60, 84, 100, 250, 500 and 1000.

6.6 Special precautions for disposal

Not Applicable

7 MARKETING AUTHORISATION HOLDER

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PL 42976/0012

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07/08/2020