APPROVED
By Geeta at 11:53 am, Jan 24, 2019

1 NAME OF THE MEDICINAL PRODUCT

Bendroflumethiazide 2.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Bendroflumethiazide 2.5mg

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets.

White to off white circular, biconvex, uncoated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bendroflumethiazide is indicated for:

1. Cases where the reduction of fluid retention by diuresis is required; oedema of cardiac, renal or hepatic origin and iatrogenic oedema
2. 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

For oral administration

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, 5-10 mg in the morning, daily or on alternate days; maintenance dose 5-10 mg one to three times weekly

Hypertension
The usual dose is 2.5 mg – 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.

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

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

- Sensitivity to bendroflumethiazide or other sulphonamide-derived drugs. .
- Severe renal insufficiency or anuria
- Severe hepatic impairment (risk of precipitation of encephalopathy)
- Addison's disease.
- Refractory Hyperkalemia, hyponatremia or hypercalcemia
- Symptomatic hyperuricemia
- Bendroflumethiazide tablets should not be administered with lithium carbonate.

4.4 Special warnings and precautions for use

Continued or intensive use of bendroflumethiazide may produce potassium depletion. A potassium chloride supplement is recommended in these circumstances. Potassium replacement or conservation is also likely to be necessary in patients at risk from the cardiac effects of hypokalaemia, such as those with severe heart disease, those taking digitalis preparations or high doses of diuretics and in patients with severe liver disease. 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. Magnesium depletion has also been implicated as a risk factor for arrhythmias.
Use with caution in renal impairment (severe renal insufficiency is a contraindication to use, see 4.3). Use with caution in hepatic impairment (severe hepatic impairment is a

contraindication to use, see 4.3). The risk of hypokalaemia is increased in patients with hepatic cirrhosis.
In seriously ill patients, reversible increases in blood urea have been reported accompanying vigorous diuresis, hepatic cirrhosis, ascites and metabolic alkalosis or those with resistant oedema. Serum electrolyte and blood urea levels should be carefully monitored in these patients.
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(see also 4.8 Undesirable Effects, Electrolyte Balance) 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.
Use of thiazides may aggravate diabetes mellitus and gout (see 4.8 Undesirable Effects, Endocrine & Metabolic subsections).
Exacerbation or activation of systemic lupus erythematosus by thiazides has been reported.
Caution is required in patients with severe asthma, as hypokalaemia associated with beta$_2$-agonist therapy can be potentiated by concurrent use of diuretics.

Aggravates diabetes mellitus and gout increased risk of hypomagnesaemia in alcoholic cirrhosis

Caution is required when treating patients with porphyria.

Patients taking pimozide or thioridazine. (see section 4.5)

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

- **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.

- **Analgesics**: Some Non-steroidal anti-inflammatory drugs (NSAIDs), notably indometacin, may attenuate the diuretic, natriuretic and antihypertensive effects of diuretics. Diuretics may increase the risk of nephrotoxicity of NSAIDs.

- **Anion exchange resins**: Colestipol and colestyramine reduce absorption of thiazides and should be given at least 2 hours apart , .

- **Anti-arrhythmics:** cardio toxicity 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.

- **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.
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- **Antidiabetics***:* Bendroflumethiazide may antagonise the hypoglycaemic effects of antidiabetic drugs including insulin possibly necessitating adjustment of the dose of the antidiabetic agent. 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 Antigout agents: Potential for increased toxicity and hypersensitivity/allergic reactions with concomitant use of allopurinol and thiazide diuretics.

- **Antihistamines**: Bendroflumethiazide-induced hypokalaemia may increase the risk of arrhythemias with drugs that prolong the QT interval, such as astemizole and terfenadine

- **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

- 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**: Bendroflumethiazide -induced hypokalaemia may increase the risk of arrhythmias with drugs that prolong the QT interval, such as halofantrine

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- **Antipsychotics**: Diuretic-induced Hypokalaemia increases the risk of ventricular arrhythmias with pimozide or sertindole concomitant use should be avoided. Enhanced hypotensive effect may occur when phenothiazines and thiazide diuretics are used concomitantly.

- **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.

- **Cardiac Glycosides**: Potential for diuretic-induced hypokalaemia to increase the risk of cardiac glycoside toxicity. Diuretic-induced hypokalaemia intensifies the effect of cardiac glycosides on cardiac muscle and treatment with cardiac glycosides may have to be temporarily suspended.

- **Ciclosporin**: Increased risk of nephrotoxicity and/or hypermagnesaemia with concomitant use of ciclosporin and thiazide diuretics, such as bendroflumethiazide.

- **Corticosteroids**: Increased risk of thiazide-induced hypokalaemia, mainly with the naturally occurring corticosteroids such as cortisone and hydrocortisone. The synthetic corticosteroids have a much less marked potassium-losing effect. Fluid retention associated with corticosteroid use may antagonise the diuretic/antihypertensive effect

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

- **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 dose of the digoxin should be temporarily reduced and a potassium supplement given to restore stability

- **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**: Thiazide diuretics may increase the risk of hypercalcaemia with toremifene. There is an increased risk of hyponatraemia when thiazides (bendroflumethiazide) are used concomitantly with aminoglutethimide.

- **Lithium**: Lithium may accumulate as a result of reduced renal clearance (see 4.3 Contraindications).

- **Muscle relaxants**: Lithium may accumulate as a result of reduced renal clearance (see 4.3 Contraindications). Enhanced hypotensive effect may occur with tizanidine. Diuretic-induced hypokalaemia may potentiate the blockade of non-depolarising neuromuscular blocking agents.

- **Nitrates**: Enhanced hypotensive effect may occur when nitrates and thiazide diuretics are used concomitantly.

- **Oestrogens and progestogens**: Oestrogens and combined oral contraceptives antagonise the diuretic effect of thiazides

- **Prostaglandins**: Hypotensive effect may be potentiated by alprostadil.

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

- **Vitamins**: See under Calcium salts & Vitamins.

- **Sympathomimetics**: Increased risk of hypokalaemia with thiazide diuretics and high doses of $beta_2$ sympathomimetics. (See 4.4 Special warnings and precautions for use, use of $beta_2$-agonists in severe asthma.

- **Ulcer healing drugs**: Potential for severe hypokalaemia with carbenoxolone. Patients should be monitored and given potassium supplements when required.

- **Drug/Laboratory tests:** Because thiazides may affect calcium metabolism, bendroflumethiazide may interfere with tests for parathyroid function. Bendroflumethiazide should be stopped before parathyroid function is tested .
- **Alcohol, barbiturates or opioids**: Postural hypotension associated with therapy may be enhanced by concomitant ingestion of alcohol, barbiturates or opioid.

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

4.6 Fertility, pregnancy and lactation

Expectant mothers using bendroflumethiazide may be at increased risk of acute haemorrhagic pancreatitis, reductions in maternal blood volume may decrease placental perfusion. Neonatal jaundice, thrombocytopenia, and severe electrolyte imbalances, including hypokalaemia and hyponatraemia have been reported in newborn infants. Cases are rare and should not prevent the use of bendroflumethiazide when indicated in pregnancy. Bendroflumethiazide is secreted in mother's milk; therefore breast feeding should be avoided. Treatment with large doses of thiazides may suppress lactation

4.7 Effects on ability to drive and use machines

Dizziness, drowsiness, postural hypotension and mental confusion may occur. This may impair ability to drive or operate machinery

4.8 Undesirable effects

Blood and lymphatic system disorders: Blood dyscrasias may occur, including thrombocytopenia and rarely neutropenia, leucopenia, agranulocytosis or aplastic anaemia. A few cases of serious thrombocytopenia (neonatal thrombocytosis when given in late pregnancy), agranulocytosis or aplastic anaemia have been reported.

Immune system disorders: Hypersensitivity reactions may occur and may involve pruritus, skin rashes, pulmonary oedema, pneumonitis, toxic epidermal necrolysis and anaphylaxis (see also Skin and subcutaneous tissue disorders below).
Endocrine disorders: Thiazides may cause hyperglycaemia and aggravate or unmask diabetes mellitus. Blood glucose concentrations should be monitored in patients taking antidiabetics since requirements may change (see 4.5 Interactions, Antidiabetics).

Metabolism and nutrition disorders: Blood uric acid levels may be increased with or without gout.

Electrolyte imbalance including hypochloraemic alkalosis, hypomagnesaemia, hypercalcaemia, hypokalaemia and hyponatraemia. Urinary excretion of calcium may be reduced and the potential for hypercalcaemia may be increased (use in pre-existing hypercalcaemia is contraindicated). Hyponatraemia as a complication is rare, but

constitutes a medical emergency, as onset may be rapid. The symptoms of hyponatraemia may be non-specific and include nausea, lethargy, weakness, mental confusion, irritability, muscle cramps and anorexia, but it may be an important cause of morbidity. Severe sequelae of hyponatraemia include tonic-clonic seizures and clinical features resembling subarachnoid haemorrhage (see also 4.4 Special warnings & precautions for use).

Plasma lipids may be altered in patients taking bendroflumethiazide.

Psychiatric disorders: Reduced libido

Nervous system disorders: Headache, dizziness, paraesthesia. Drowsiness may occur and may be associated with electrolyte imbalance

Cardiac disorders: Postural hypotension

Vascular disorders: Vasculitis

Respiratory, thoracic and mediastinal disorders:
Pneumonitis, pulmonary oedema

Gastrointestinal disorders: Diarrhoea, constipation. Other mild gastrointestinal effects, including nausea, vomiting, dry mouth and thirst may be associated with hypokalaemia. Pancreatitis.

Hepatobiliary disorders: Cholecystitis; cholestasis

Skin and subcutaneous tissue disorders: Rash, photosensitivity, which may persist after thiazide withdrawal. Eruptions resembling lichen planus and subacute cutaneous lupus erythematosus may be due to photosensitivity reactions. Erythema multiforme, pseudoporphyria

Renal and urinary disorders: Acute interstitial nephritis, non-opaque urate calculi. Oliguria may occur and may be associated with electrolyte imbalance

Reproductive system and breast disorders:
Impotence

Investigations: Increased triglyceride, total cholesterol, low-density and very-low-density lipoprotein cholesterol concentrations
Hypokalaemia, hypomagnesaemia, hyponatraemia, hypercalcaemia, hypochloraemic alkalosis. Hypokalaemia may result in polyuria, malaise, muscle weakness or cramp, dizziness, nausea, anorexia or vomiting

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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of overdosage include nausea, vomiting, diarrhoea, diuresis, dehydration, dizziness, weakness, muscle cramps, increased frequency of micturition with polyuria and thirst. Extreme cases may show depletion of intravascular volume, hypotension and peripheral circulatory failure. Mild hypoglycaemia and hypokalaemia are likely to be present if dieresis is profound.

CNS depression (*eg* 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: diuretic, ATC code: C03AA01

Bendroflumethiazide is a thiazide diuretic.

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. 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.. Diuresis is initiated in about 2 hours and lasts for 12-18 hours or longer About 30% is excreted unchanged in the urine. The onset of the hypotensive action is generally three or four days.

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

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

Anhydrous Lactose

Talc

Pregelatinised starch

Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/PVDC Aluminium foil blisters: 3years
HDPE containers: 18 months

6.4 Special precautions for storage

PVC/PVDC Aluminium foil blisters: Do not store above 25ºC. Store in the original package
HDPE containers: Do not store above 25ºC. Keep the container tightly closed.

6.5 Nature and contents of container

PVC/PVDC Aluminium foil blister, pack sizes of 14, 28, 56, 84 tablets.
HDPE tablet containers, pack sizes of 50, 100, 250, 500, 1000 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited
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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0082

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/09/2011

10 DATE OF REVISION OF THE TEXT

23/01/2019