NEW ZEALAND DATA SHEET

1 NAME OF THE MEDICINE

Arrow-Bendrofluazide 2.5, 2.5 mg, tablets

Arrow-Bendrofluazide 5, 5 mg, tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg or 5 mg of bendroflumethiazide (also known as bendrofluazide).

Excipient with known effect: lactose

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Tablets 2.5 mg: White to almost white, circular, biconvex, uncoated tablets.

Tablets 5 mg: White to almost white, circular, flat, bevelled edged uncoated tablets with '5' embossed on one side.

Do not halve the tablets. Dose equivalence when the tablet is divided has not been established.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bendroflumethiazide is indicated in the treatment of oedema associated with conditions such as: congestive heart failure, nephrotic syndrome and cirrhosis of the liver.

Bendroflumethiazide is indicated in the treatment of essential hypertension where it may be used as the sole antihypertensive agent, or as an adjunct to other medicines whose action it potentiates.

4.2 Dose and method of administration

Adults

When bendroflumethiazide is added to other antihypertensive agents, the dosage of the latter can usually be reduced gradually as bendroflumethiazide takes effect.

Oedema

5 mg given orally once daily in the morning usually produces the desired effect without diuresis interfering with sleep, but this dose can be increased to 10 mg if required. During the first few days of treatment there is usually a large increase in urinary volume, which diminishes as treatment continues.

Essential hypertension

2.5 mg to 10 mg once daily, alone or in conjunction with other antihypertensive agents.

Maintenance

Many patients will respond adequately to a daily dose of 2.5 mg or 5 mg on only two or three days in the week.

Children

For children up to 12 years of age, 50-100 mcg/kg bodyweight daily.

4.3 Contraindications

Severe renal or hepatic failure, hypersensitivity to the product or other sulphonamide-like medicines, Addison's disease, diabetic keto-acidosis and hypercalcaemia.

Treatment with lithium carbonate.

4.4 Special warnings and precautions for use

When treatment with bendroflumethiazide is intensive or continuous, periodic estimations of serum electrolytes (especially potassium) should be carried out. Some loss of potassium may occur and, in these circumstances, potassium chloride supplements may be required in the following cases:

- if the patient is vomiting, has diarrhoea or is suffering from an acute febrile or chronic illness (especially cirrhosis of the liver or heart failure).

- to prevent hypokalaemia, possible arrhythmias and other ECG changes in patients receiving digitalis especially if diuretic treatment is prolonged.

- in patients at risk of myocardial infarction.

- in patients admitted for cardiac surgery.

- in patients receiving concurrent therapy with carbenoxolone or corticosteroids.

Potassium depletion may cause polyuria, malaise, muscle weakness or cramp, decreased tendon reflexes, anorexia, dizziness, nausea or vomiting. Also, sensitivity to digitalis may increase and signs of overdosage appear. Prolonged potassium deficiency may induce chronic pyelonephritis.

Potassium supplements must not be given in renal insufficiency complicated by hypokalaemia. In renal insufficiency, renal function should be monitored. In prolonged therapy it is necessary to test for glycosuria and investigate polyuria. The possibility of magnesium depletion should be considered.

In cirrhosis of the liver, thiazides may precipitate hepatic encephalopathy. The risk of hypomagnesaemia is increased in alchoholic 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.

Thiazides may aggravate existing diabetes mellitus and cause symptoms in patients with latent disease. Bendrofluazide may impair control of diabetes in patients receiving sulphonylureas. Thiazides should be used with caution in systemic lupus erythematosus.

Caution is required when treating patients with porphyria.

Serum uric acid levels may be raised in some patients, with or without gout.

Thiazides may cause or aggravate hyperlipidaemia.

Elderly

The elderly are sensitive to the effects of thiazides on blood pressure and electrolytes. Administration of supplementary potassium is particularly important in the elderly. Patients with prostatic hypertrophy may develop acute urinary retention.

4.5 Interaction with other medicines 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.

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. *Antiarrhythmics:* The cardiotoxicity of disopyramide, amiodarone, flecainide and quinidine is increased if hypokalaemia occurs following the administration of bendroflumethiazide. The actions of lidocaine and mexiletine are antagonised by hypokalaemia.

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.

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

Antiepileptics: There is an increased risk of hyponatraemia when bendroflumethiazide and carbamazepine are take concurrently.

Antifungals: The risk of hypokalaemia is increased when amphotericin and bendroflumethiazide are taken concurrently.

Antihypertensives: Bendroflumethiazide may enhance the antihypertensive effect of ACE inhibitors and angiotensin-II antagonists. There is an increased risk of first dose hypotension if prazosin is given to a patient taking bendroflumethiazide.

Antipsychotics: Hypokalaemia increases the risk of ventricular arrhythmias with pimozide or thioridazine so concomitant use should be avoided.

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.

Calcium channel blockers and peripheral vasodilators: The hypotensive effect of calcium channel blockers and moxisylyte may be enhanced when co-administered with bendroflumethiazide.

Corticosteroids: Corticosteroids may exacerbate hypokalaemia associated with bendroflumethiazide and its diuretic activity may be antagonised.

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

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.

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.

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.

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.

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.

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.

Vitamins: The risk of hypercalcaemia is increased if bendroflumethiazide is given with vitamin D.

4.6 Fertility, pregnancy and lactation

Pregnancy

Diuretics are best avoided in 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.

There are rare reports of foetal and neonatal bone marrow depression, thrombocytopenia, electrolyte imbalance, hypoglycaemia and jaundice.

Expectant mothers who receive thiazide diuretics may be at increased risk from acute haemorrhagic pancreatitis.

In parturition, thiazides may cause uterine inertia and delay the onset of labour.

Thiazides are only indicated in pregnancy if oedema complicates a pathological lesion and, even then, after assessing risk versus benefit including the undesirability of administering medicines in the first trimester.

Breast-feeding

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

Fertility

No information available.

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 frequencies of adverse events are ranked according to the following: 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).

Blood and lymphatic system disorders

Not known:	Blood dyscrasia including agranulocytosis, aplastic anaemia, thrombocytopenia and leucopenia

Metabolism and nutrition disorders

Not known:	Hypokalaemia, hypomangnesaemia, hyponatraemia, hypercalcaemia[1], hypochloraemic alkalosis. Hypokalaemia may result in polyuria, malaise, muscle weakness or cramp, dizziness, nausea, anorexia or vomiting

Nervous system disorders

Not known:	Dizziness

Vascular disorders

Not known:	Postural hypotension

Respiratory, thoracic and mediastinal disorders

Not known:	Pneumonitis, pulmonary oedema

Gastrointestinal disorders

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

Hepatobiliary disorders

Not known:	Intrahepatic cholestasis

Skin and subcutaneous tissue disorders

Not known:	Rashes (including exfoliative dermatitis), photosensitivity

Reproductive system and breast disorders

Not known:	Impotence (reversible on discontinuing the drug)

Investigations

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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. CNS depression (eg. drowsiness, lethargy and coma) may occur without cardiovascular or respiratory depression. Hypokalaemia and mild hypoglycaemia are likely to be present if diuresis is profound.

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 the administration of sodium chloride. Cathartics should be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Thiazide diuretics, ATC code: C03AA01

Mechanism of action

Bendroflumethiazide inhibits the renal tubular absorption of salt and water. Sodium and chloride ions are excreted in equivalent proportions, and there is little or no disturbance of the acid/base equilibrium. There is no important effect upon carbonic anhydrase. Bendroflumethiazide initiates diuresis in about 2 hours and maintains a steady diuresis lasting for about 12 hours.

The mechanism whereby the thiazides exert their antihypertensive effect has not been clearly established. In non-oedematous patients there may be little noticeable diuretic effect.

5.2 Pharmacokinetic properties

The following data apply to Bendroflumethiazide tablets.

Since bendroflumethiazide is completely absorbed from the gastrointestinal tract and only about 30% is excreted unchanged in the urine, the majority of an oral dose being eliminated by non-renal mechanisms, it has been inferred that bendroflumethiazide is extensively metabolised.

It has been suggested that metabolites, some of which may be active, accumulate during chronic treatment and compete with bendroflumethiazide for pathways of tubular secretion. Bendroflumethiazide is estimated to have a plasma half-life of about 3 or 4 hours, its biological half-life being much longer. It is 94% bound to human serum albumin in vitro. The time to reach peak concentration is 2 to 2.5 hours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, pregelatinised starch, purified talc and stearic acid.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25°C. Protect from heat and light.

Store in the original package.

6.5 Nature and contents of container

Blister packs containing 14 or 28 tablets.

HDPE containers containing 500 or 1000 tablets.

Not all pack sizes or pack types may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9 DATE OF FIRST APPROVAL

10 December 2009

10 DATE OF REVISION OF THE TEXT

6 May 2019

Summary table of changes

Section Changed	Summary of new information
4.4, 4.5, 4.6, 4.7, 4.8, 4.9	Updated safety information in accordance with Teva CCSI No. 186/03/12/18