1.3 Product Information

1.3.1 Summary Product Characteristics (SPC):

Enclosed

Module I Administrative Information
Product Name: Bedozym 5 - Bendrofluazide Tablets BP 5 mg

1.3.1 Summary Product Characteristics

1. **Name of the proprietary product:** Bedozym 5

   Name of the nonproprietary International Product: Bendrofluazide Tablets BP 5 mg

   Route of Administration: Oral

2. **Qualitative and Quantitative:** 100,000 Tablets

UNIT FORMULA

Sr. No	Ingredients	Grade	Rationale	Label Claim	Quantity per Unit (mg)	Quantity per Batch (Actual-Kg)
Mixing						
1.	Bendroflumethiazide	BP	Active	5 mg	5.00	0.500
2.	Microcrystalline Cellulose	BP	Disintegrant	-----	22.00	2.20
3.	Maize Starch	BP	Diluent	-----	126.9	12.69
4.	Lactose monohydrate	BP	Diluent	-----	30.00	3.000
5.	Colloidal anhydrous silica	BP	Lubricant	-----	0.600	0.060
6.	PVP K -30 (Povidone)	BP	Binder	-----	4.000	0.400
7.	Methyl Paraben	BP	Preservative	-----	0.400	0.0400
8.	Propyl Paraben	BP	Preservative	-----	0.080	0.0080
9.	*Isopropyl Alcohol	BP	Solvent	-----	88.00	8.800
10.	Magnesium Stearate	BP	Lubricant	-----	2.000	0.200
11.	Purified Talc	BP	Lubricant	-----	2.000	0.200
12.	Sodium Starch Glycolate	BP	Disintegrant	-----	4.000	0.400
13.	Colloidal anhydrous silica	BP	Lubricant	-----	3.000	0.300
	Total weight of tablets				**200.0 mg**	**20.00 kg**

Where,

BP = British Pharmacopoeia
IH = In House

3.0 PHARMACEUTICAL DOSAGE FORM

Oral Solid Dosage Form

4.0 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:

5-10mg daily in the morning initially. Maintenance: usually 2.5mg-5mg on only two or three days in the week. A single dose may be sufficient.

Essential Hypertension:

2.5mg in the morning. Doses above 2.5mg are rarely necessary. Bendroflumethiazide is used concurrently with other specific hypotensive agents, the dosage of such agents should be reduced and then adjusted as necessary.

Pre-menstrual syndrome:

2.5 mg each morning for seven days before the period is due.

Elderly

Particular caution is needed in the elderly because of their susceptibility to electrolyte imbalance. Lower initial doses should be used and electrolyte balance and renal function should be carefully monitored.

Children under 12 years:

Oedema:

Up to 400µg per kg body weight daily initially, reducing to 50-100µg per kg for maintenance. A more appropriate dosage form may be required.

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

• Bendrofluemthiazide may precipitate or aggravate diabetes mellitus and may impair control of diabetes in patients receiving sulphonyureas.

• 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 balance 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 dycrasias. 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.

• 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)

• Bendroflumethiazide tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose – galactose malabsorption should not take this medicine.

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.

4.5 Interaction with Other Drugs, Other Forms of Interactions

• *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 hypokalemia is increased when amphotericin and bendroflumethiazide are taken concurrently.

• *Antifungals:* The risk of hypokalamia is increased when amphotericin and 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 bendoflumethiazide 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 bendroflumethazide 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 and carbamezapine 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: Bendroflumethazide may enhance the nephrotoxicity of NSAIDs. Indometican 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 vasodialtors:* 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 bendroflumethiaxide and the anion exchange resin.

4.6 Fertility, pregnancy and lactation

Bendrofluemthiazide 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.

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

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

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.

Blood and lymphatic system disorders:

Rarely, blood dyscrasias, including agranulocytosis, aplastic anaemia, thrombocytopenia and rarely neutropenia, leucopenia have been reported.

Immune system disorders: Hypersensitivity reactions may occur and may involve pruritus, skin rashes(including exfoliative dermatitis), photosensitivity, pulmonary oedema, pneumonitis, toxic epidermal necrolysis and anaphylaxis (see also Skin and subcutaneous tissue disorders below).

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

Electrolyte imbalance including hypochloraemic alkalosis, hypomagnesaemia, 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).

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

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

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 and breast disorders: Impotence.
Investigations: Increased triglyceride, total cholesterol, low-density and very-low-density lipoprotein cholesterol concentrations.

4.9 Overdose

Symptoms of overdosage include nausea, vomiting, diarrhoea, diuresis, dehydration, hypotension, 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. 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 classification & ATC Classification:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Thiazide diuretics ATC CODE; CO3 AA01
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: Bendrofluemthiazide 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

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:

Microcrystalline Cellulose
Maize Starch
Lactose monohydrate
Colloidal anhydrous silica
PVP K -30 (Povidone)
Methyl Paraben
Propyl Paraben
Isopropyl Alcohol
Magnesium Stearate
Purified Talc
Sodium Starch Glycolate

6.2 Incompatibilities: Not Applicable

6.3 Shelf life: 36 months from the date of manufacturing.

6.4 Special precautions for storage

Do not store above 30°C, protect from light

6.5 Nature and contents of container

2 X 14 Tablets in Alu-PVC Blister. Such 2 blisters are packed in a carton along with package insert.

6.6 Special precautions for disposal

No special requirements

6.7 Marketing Authorization Holder:

M/S. ZMC INTERNATIONAL LIMITED
7A, NIGER STREET,KANO ,
KANO STATE, NIGERIA

6.8 Marketing Authorization Number: ---

6.9 Date of first Authorization /renewal of the authorization: ---

6.10 Date of revision of text: