1.3 Product Information

1.3.1 Summary Product Characteristics (SPC):

Enclosed

1.3.1 Summary Product Characteristics

Name of the proprietary product: ZORACTONE

Name of the nonproprietary International Product:

Spironolactone tablets BP 25 mg

Route of Administration: Oral

Qualitative and Quantitative

Label Claim:

Each film coated tablet contains:

Spironolactone BP	25 mg
Excipients	q.s.

Colour: Sunset Yellow FCF

Module I Administrative Information
Product Name: ZORACTONE (Spironolactone tablets BP 25 mg)

Batch Formula
COMPOSITION
BATCHSIZE: 1,00,000 Tablets

Sr. No.	Ingredients	Specification	Label claim	Unit Formula (mg)	Overages (%)	Batch Formula (kg)	Functions
DRY MIXING							
1	Spironolactone	BP	25 mg	25.000		2.500	Active Ingredient
2	Calcium Sulfate Dihydrate	BP		50.000		5.000	Diluent
3	Microcrystalline Cellulose	BP		58.000	3.00 #	5.974	Diluent
4	Sodium Starch Glycolate	BP		8.000		0.800	Disintegrant
BINDING STAGE							
5	Lactose Monohydrate	BP		30.125		3.012	Binder
6	Povidone (P.V.P.K-30)	BP		4.300		0.430	Binder
7	Iso propyl alcohol	BP		q.s.		q.s.	Solvent
LUBRICATION							
8.	Sodium Starch Glycolate	BP		3.500		0.350	Disintegrant
9.	Colloidal anhydrous silica	BP		0.575		0.057	Glidant
10.	Magnesium Stearate	BP		0.500		0.050	Lubricant
Uncoated Tablet weight				**180.00 mg**		**18.173 kg**	
COATING STAGE							
11	Sunset yellow FCF	IH		5.000		0.500	Colouring agent
12	Isopropyl Alcohol	BP		0.034 ml		3.400 Lit	Solvent
13	Methelene chloride	BP		0.051 ml		5.100 Lit	Solvent
Total Weight Tablet				**185.00 mg**		**18.673 kg**	

Where, BP: British Pharmacopoeia, IH: In-House

Quantity of Microcrystalline Cellulose to be taken to compensate the average weight of tablet.

Quantity of Microcrystalline Cellulose (PH 102) to be taken as 3.00 % overages due to loss on drying.

3. Pharmaceutical Form: Oral Tablets

4. Clinical Particulars:

4.1 Therapeutic Indications:
• Oedema associated with congestive heart failure
• Severe heart failure, (NYHA III-IV)
• As an adjuvant in treatment of resistant hypertension
• Nephrotic syndrome
• Liver cirrhosis with ascites and oedema
• Diagnosis and treatment of primary hyperaldosteronism (Conn's syndrome)
Children should only be treated under guidance of a paediatric specialist. There is limited paediatric data available.

4.2 Posology and method of administration:
Posology
Adults
The dosage should be determined individually depending on the condition and the degree of diuresis required. Dosage up to100 mg daily may be administered as a single dose or in divided doses.
Oedema associated with congestive heart failure
For management of oedema an initial daily dose of 100 mg of spironolactone administered in either single or divided doses is recommended, but may range from 25 to 200 mg daily. Maintenance dose should be individually determined.
Severe heart failure (NYHA Class III-IV)
Treatment in conjunction with standard therapy should be initiated at a dose of spironolactone 25 mg once daily if serum potassium is $\leq$ 5.0 mEq/L and serum creatinine is $\leq$ 2.5 mg/dL (221 µmol/L). Patients who tolerate 25 mg once daily may have their dose increased to 50 mg once daily as clinically indicated. Patients who do not tolerate 25 mg once daily may have their dose reduced to 25 mg every other day.
Resistent Hypertension
The starting dose for spironolactone should be 25mg daily in a single dose; the lowest effective dose should be found, very gradually titrating upwards to a dose of 100mg daily or more.
Nephrotic syndrome
Usual dose is 100-200mg/day. Spironolactone has not been shown to be anti-inflammatory, nor to affect the basic pathological process. Its use is only advised if glucocorticoids by themselves are insufficiently effective.
Hepatic cirrhosis with ascites and oedema
The starting dose is 100-200 mg per day, e.g. based on Na+/K+ ratio. If the response to 200 mg spironolactone within the first two weeks is not sufficient, furosemide is added and if necessary, the spironolactone dose is increased stepwise up to 400 mg per day. Maintenance dosage should be individually determined.
Diagnosis and treatment of primary aldosteronism

If primary hyperaldosteronism is suspected, spironolactone is given at a dose of 100 – 150 mg**,** or up to 400 mg daily. In the event of rapid onset of a strong diuretic and antihypertensive effect, this is a clear indication of elevated aldosterone production. In this case, 100 – 150 mg daily is administered for 3 – 5 weeks prior to surgery. If surgery is not an option, this dose is often sufficient to maintain blood pressure and potassium concentration at normal levels. In exceptional cases, higher doses are necessary, but the lowest possible dosage should be found.

Paediatric population

Initial daily dosage should provide 1-3 mg of spironolactone per kilogram body weight, given in divided doses. Dosage should be adjusted on the basis of response and tolerance. The tablet may be ground or crushed and then suspended in water to make it easier to take.

Children should only be treated under guidance of a paediatric specialist. There is limited paediatric data available.

The Elderly

It is recommended that treatment is started at the lowest possible dose, then titrated with higher doses until the optimum effect is achieved. Caution is required, in particular in renal dysfunction.

Method of administration

The tablets should be taken with meals. Daily dosages in excess of 100 mg should be given in several divided doses.

4.3 Contraindications

• Hypersensitivity to the active substance(s) or to any of the excipients used.
• Severe renal insufficiency (eGFR <30 mL per minute per 1.73 m^2), acute or progressive kidney disease (whether or not this is accompanied by anuria)
• Hyponatraemia
• Hyperkalaemia (serum potassium level > 5.0 mmol/L) at initiation
• Concomitant use of potassium-sparing diuretics (including eplerenone) or potassium-supplements, or dual-RAAS blockade with the combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB)

Spironolactone is contraindicated in paediatric patients with moderate to severe renal impairment.

4.4 Special warnings and precautions for use

Fluid and electrolyte balance

During long-term therapy with spironolactone, fluid and and electrolyte status should be regularly monitored, especially in elderly patients. Administration of spironolactone is not recommended if plasma potassium levels are elevated and contra-indicated in severe renal insufficiency. During treatment with spironolactone, severe hyperkalaemia can occur, which may result in cardiac arrest (sometimes fatal) in patients with severe renal dysfunction who are receiving concomitant treatment with potassium supplements.

Hyperkalaemia may be accompanied by paraesthesia, weakness, mild paralysis or muscle spasms and is difficult to distinguish clinically from hypokalaemia. ECG changes may be the first sign of disturbed potassium balance, although hyperkalaemia is not always accompanied by an abnormal ECG.

Combination with potent potassium-sparing diuretics such as triamterene and amiloride is contra-indicated in order to prevent hyperkalaemia and care should be taken to avoid administration of extra potassium

Impaired renal function
Potassium levels should be monitored regularly in patients with impaired renal function, including diabetic microalbuminuria. The risk of hyperkalaemia increases with decreasing renal function. Therefore, these patients should be treated with caution.
Severe hepatic insufficiency
Caution is required in patients with hepatic disorders due to the risk of hepatic coma.
Carcinogenicity
Animal studies have shown that at high doses and after long-term use, spironolactone induces tumours. The significance of these data for clinical application is unclear. However, the benefits of therapy should be weighed against the possible long-term harm before initiating long-term use of spironolactone in young patients.
Lactose
This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Paediatric population
Potassium-sparing diuretics should be used with caution in hypertensive paediatric patients with mild renal insufficiency because of the risk of hyperkalaemia.
Concomitant use of medicinal products known to cause hyperkalaemia with spironolactone may result in severe hyperkalaemia.

4.5 Interaction with other medicinal products and other forms of interaction
Interactions affecting spironolactone
Combinations causing hyperkalaemia
Concomitant use of potassium-sparing diuretics (including eplerenone) or potassium-supplements , or dual-RAAS blockade with the combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) is contraindicated because of the risk of hyperkalaemia.
The use of ACE inhibitors in combination with spironolactone may be accompanied by hyperkalaemia, especially in patients with impaired renal function. Concomitant use requires careful dosing and close monitoring of the electrolyte balance.
Spironolactone and ciclosporin coadministration not recomended, as both increase serum potassium level and possible serious life-threatening interactions.
Heparin, low molecular weight heparin:
Concomitant use of spironolactone with heparin or low molecular weight heparin may lead to severe hyperkalemia. Increased diuresis has been observed during concomitant use of spironolactone and heparin.
Non-Steroidal Anti-Inflammatory Drugs
Acetyl salicylic acid and indomethacin may attenuate the diuretic action of spironolactone due to inhibition of intrarenal synthesis of prostaglandins. Hyperkalemia has been associated with the use of indomethacin in combination with potassium-sparing diuretics.
Interactions affecting other medicinal products
Anti-coagulants
Spironolactone reduces the effect of anticoagulants.
Noradrenalin
Spironolactone reduces the vasoconstrictive effects of noradrenaline.

Anti-hypertensives
Spironolactone can potentiate the effect of antihypertensive agents. The dosage of such drugs, in particular ganglion-blocking drugs, can often be halved when spironolactone is added to the therapy.
Lithium
Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.
Digoxin
Spironolactone has been shown to increase the half-life of digoxin. This may result in increased serum digoxin levels and subsequent digitalis toxicity.
Alcohol, barbiturates or narcotics
Potentiation of orthostatic hypotension may occur.
Cholestyramine
Hyperchloremic metabolic acidosis, frequently associated with hyperkalemia, has been reported in patients given spironolactone concurrently with cholestyramine.
Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalemia, may occur.
Other forms of interaction
Ammonium Chloride
Hyperchloremic metabolic acidosis, frequently associated with hyperkalemia, has been reported in patients given spironolactone concurrently with ammonium chloride (e.g. in liquorice).
Plasma Cortisone levels
Spironolactone interferes with Mattingly's fluorimetric method for determination of plasma cortisone levels.
In addition to other medicinal products known to cause hyperkalaemia concomitant use of trimethoprim / sulfamethoxazole (co-trimoxazole) with spironolactone may result in clinically relevant hyperkalaemia.

4.6 Pregnancy and Lactation:
Pregnancy
There are very limited data on the use of spironolactone during pregnancy in humans.
Experimental animal studies have shown reproductive toxicity associated with the anti-androgenic effect of spironolactone. Spironolactone should not be used during pregnancy.
Diuretics can lead to reduced perfusion of the placenta and thus to impairment of intrauterine growth and are therefore not recommended for the standard therapy for hypertension and edema during pregnancy.
Breastfeeding
Canrenone, the principal and active metabolite of spironolactone, appears in small quantities in human breast milk. Spironolactone should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from spironolactone-therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the women.
Fertility
Spironolactone may induce impotence and menstrual irregularities.

4.7 Effects on the ability to drive and use machines

No data are available on the ability to drive. Undesirable effects such as dizziness, confusion and headache may occur. The possible occurrence of these undesirable effects should be taken into account when driving or using machines.

4.8 Undesirable effects:

The undesirable effects are dependent on dose and duration of treatment.

The most common adverse effects are hyperkalaemia (9%), disorders of the reproductive system and breasts, including gynaecomastia, reported in 13% of patients (at a dose of less than 100 mg). Gynaecomastia appears to be related to both dosage level and duration of therapy and is usually reversible once treatment stops. Other very common undesirable effects include headache, digestive system disorders, diarrhoea, fatigue and drowsiness.

The undesirable effects below are classified in accordance with the following frequencies: Very common (1/10), Common (1/100, < 1/10), Uncommon (1/1,000, <1/100), Rare (1/10,000, <1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data)

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Very rare: breast cancer

Blood and lymphatic system disorders

Rare: thrombocytopenia, eosinophilia, leukopenia (including agranulocytosis)

Immune system disorders

Rare: eczema (type 1 allergic reaction), hypersensitivity

Endocrine disorders

Not known: slight androgenic effects, including hirsutism.

Metabolism and nutrition disorders

Very common: hyperkalaemia in patients with severe renal dysfunction who are receiving concomitant treatment with potassium supplements.

Common: hyponatraemia (in particular during combined intensive therapy with thiazide diuretics), hyperkalaemia in (1) patients with severe renal dysfunction, (2) patients receiving treatment with ACE inhibitors or potassium chloride, (3) the elderly, and (4) diabetic patients

Uncommon: acidity of the blood (acidosis) in patients with liver problems

Rare: insufficient fluid in the tissues (dehydration), porphyria, temporary increase in nitrogen levels in the blood and urine, hyperuricemia (may lead to gout in predisposed patients)

Not known: reversible hyperchloraemic metabolic acidosis – usually accompanied by hyperkalaemia has been reported in some patients with decompensated hepatic cirrhosis, even where renal function was normal.

Psychiatric disorders

Uncommon: confusion

Nervous system disorders

Very common: headache

Common: weakness, lethargy in patients with cirrhosis, tingling (paraesthesia)

Rare: paralysis, paraplegia of the limbs due to hyperkalaemia

Not known: dizziness, ataxia

Vascular disorders

Very rare: inflammation of the vessel walls (vasculitis)

Not known: mild hypotension

Gastrointestinal disorders

Very common: indigestion, diarrhoea
Common: nausea and vomiting
Very rare: gastric inflammation, gastric ulcers, intestinal haemorrhage, cramps
Hepatobiliary disorders
Very rare: hepatitis
Skin and subcutaneous tissue disorders
Uncommon: skin rash, urticaria, erythema, chloasma, pruritus, exanthema
Very rare: alopecia, eczema, erythema annulare centrifugum (EAC), hypertrichosis
Not known: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), Pemhigoid
Musculoskeletal and connective tissue disorders
Uncommon: muscle spasms, leg cramps
Very rare: systemic lupus erythematosus (SLE), Osteomalacia
Renal and urinary disorders
Uncommon: elevated serum creatinine levels
Very rare: acute renal failure
Reproductive system and breast disorders
Very common: Men: reduced libido, erectile dysfunction, impotence, enlargement of the mammary glands (gynaecomastia);
Women: breast disorders, tenderness of the breasts, menstrual disorders, deepening of the voice (in many cases irreversible)
Common: Women: changes in vaginal secretions, reduced libido, absence of periods (amenorrhoea),
post-menopausal bleeding
General disorders and administration site conditions
Very common: fatigue, drowsiness
common: malaise
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.

4.9 Overdose:
Overdose can manifest itself in the form of nausea and vomiting, and (more rarely) by drowsiness, confusion, skin rash or diarrhoea.
In addition, infertility can occur at very high doses (450 mg/day).
Hyponatraemia, or hyperkalaemia may be induced , but these effects are unlikely to be associated with acute overdosage. Symptoms of hyperkalaemia may manifest as paraesthesia, weakness, flaccid paralysis or muscle spasm and may be difficult to distinguish clinically from hypokalaemia. Electrocardiographic changes are the earliest specific signs of potassium disturbances. No specific antidote has been identified. Improvement may be expected after withdrawal of the drug.
If electrolyte balance disturbance and dehydration occur,treatment is symptomatic and supportive and may include replacement of fluids and electrolytes may be indicated. For hyperkalaemia, reduce potassium intake, administer potassium-excreting diuretics, intravenous glucose with regular insulin or oral ion-exchange resins.

5. Pharmacological Particulars:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diuretics
ATC code: C03DA01

Spironolactone is a steroid with a structure resembling that of the natural adrenocorticoid hormone, aldosterone. It acts as a competitive inhibitor of aldosterone and acts on the distal portion of the renal tubule thereby increasing sodium and water excretion and reducing potassium excretion. It is classed as a potassium sparing diuretic or aldosterone antagonist.

5.2 Pharmacokinetic properties

Absorption – Spironolactone is incompletely but fairly rapidly absorbed from the gastrointestinal tract and the extent of absorption will depend on the particle size and formulation and is improved after food. Bioavailability is estimated from 60 to 90%. Time to peak plasma concentration is approximately one hour.
Distribution – Although the plasma half life of spironolactone itself is short (1.3 hours) the half lives of the active metabolites are longer (ranging from 2.8 to 11.2 hours).
Spironolactone is estimated to be 90% protein bound. Volume of distribution, extent of tissue accumulation and ability to cross the blood brain barrier are not known. Spironolactone or its metabolites may cross the placental barrier and canrenone is secreted breast milk. Spironolactone is known to have a slow onset of action two to three days and a slow diminishment of action.
Metabolism – The main site of biotransformation is the liver where it is metabolised, to 80% sulphur containing metabolities such as 7 alpha-thiomethylspironolactone and canrenone (20%). Many of these metabolities also have a diuretic-activity. Canrenone, which is an active metabolite, has a biphasic plasma half life of about 4 - 17 hours.
Elimination – Spironolactone is excreted in the urine and faeces in the form of metabolites.
The renal action of a single dose of spironolactone reaches its peak after 7 hours, and activity persists for at least 24 hours.

5.3 Pre-clinical Safety:

Carcinogenicity spironolactone has been shown to produce tumours in rats when administered at high doses over a long period of time. The significance of these findings with respect to clinical use in not certain. However the long term use of spironolactone in young patients requires careful consideration of the benefits and the potential hazard involved. Spironolactone or its metabolities may cross the placental barrier. With spironolactone, feminisation has been observed in male rat foetuses. The use of spironolactone in pregnant women requires that the anticipated benefit be weighed against the possible hazards to the mother and foetus.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Calcium Sulfate Dihydrate BP

Microcrystalline Cellulose BP

Sodium Starch Glycolate BP

Lactose Monohydrate BP

Povidone (P.V.P.K-30) BP

Iso propyl alcohol BP

Colloidal anhydrous silica BP

Magnesium Stearate BP

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

Keep out of reach of children.

6.5 Nature and contents of container

500 Tablets packed in one pack of Plastic Jar along with a 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: