1.3 Product Information

1.3.1 Summary Product Characteristics (SPC):

Enclosed

1.3 PRODUCT INFORMATION

1.3.1 Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

1.1 Name of the Medicinal Product
ZYNATAC

1.2 Strength
Ranitidine Hydrochloride USP
Eq. to Ranitidine 150 mg

1.3 Pharmaceutical Form
Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr. No.	Ingredient	Specification	Qty. in mg / Tab	Qty. in kg / Batch	Reason on inclusion
Active					
1.	Ranitidine Hydrochloride Equivalent to ranitidine	USP	167.50[$]	16.75	Active
Dry Mixing					
2.	Microcrystalline cellulose	BP	85.50	8.55	Diluent
3.	Croscarmellose sodium	BP	6.00	0.600	Disintegrant
4.	Colloidal Anhydrous Silica	BP	1.50	0.15	Disintegrant
5.	Magnesium stearate	BP	2.00	0.200	Lubricant
6.	Purified Talc	BP	2.50	0.250	Lubricant
Total Weight of Uncoated Tablet			**265.00**	**26.50**	
Film-coating					
7.	Hypromellose E15	BP	4.60	0.46	Film-former
8.	Sunset yellow FCF	IH	0.30	0.03	Colour
9.	Purified Talc	BP	0.10	0.01	Anti-adhesive
10.	Isopropyl Alcohol*	BP	q.s.	q.s.	Solvent
Total weight of Coated Tablet			**270.00**	**27.00**	

3. PHARMACEUTICAL FORM

Tablet

4. Clinical particulars

4.1 Therapeutic indications

In the treatment of duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents. Prevention of non-steroidal anti-inflammatory drug (including aspirin) associated duodenal ulcers, especially in patients with a history of peptic ulcer disease. Also indicated for the treatment of reflux oesophagitis, post-operative ulcer, Zollinger-Ellison Syndrome and other conditions where reduction of gastric acid secretion is likely to be beneficial.

Children (3 to 18 years)

• Short term treatment of peptic ulcers

• Treatment of gastro-oesophageal reflux, including reflux oesophagitis and symptomatic relief of gastrooesophageal reflux disease.

4.2 Posology and method of administration

Route of Administration: Oral

Adults (including the elderly) /Adolescent (12 years and over):

The usual initial dosage is 150 mg twice daily or 300 mg at night. This may be increased to ranitidine 300 mg twice daily, without an increased incidence of unwanted effects.

Subsequently a maintenance dose of 150 mg at night may be used. Smoking is associated with a higher rate of ulcer relapse and such patients should be advised to stop smoking. In those who fail to comply with such advice, a dose of 300 mg at night provides additional therapeutic benefit over the standard dose.

In most cases of duodenal ulcer, benign gastric ulcer and post-operative ulcer, healing occurs within 4 weeks. Healing usually occurs after a further 4 weeks in those not fully healed after the initial 4 weeks.

In ulcers following non-steroidal anti-inflammatory drug therapy, 8-12 weeks treatment may be necessary. For the prevention of non-steroidal anti-inflammatory drug associated duodenal ulcers, ranitidine 150 mg twice daily may be given concomitantly with non-steroidal anti-inflammatory drug therapy.

In the management of reflux oesophagitis the usual course of treatment is either 150 mg twice daily or 300 mg at night administered for up to a period of eight weeks or if necessary 12 weeks.

In patients with moderate to severe oesophagitis the dosage may be increased to 150 mg four times daily; alternatively 300 mg twice daily, if necessary.

For the long-term management of reflux oesophagitis, the recommended adult oral dose is 150 mg twice daily for the prevention of relapse in patients with reflux oesophagitis.

Ranitidine 150 mg film coated tablets are not indicated in patients with complications of reflux oesophagitis e.g. severe oesophageal stricture or Barratt's oesophagus.

In keeping with the recommended clinical practice, it is advisable that patients on long term maintenance therapy receive regular routine assessment by their practitioners.

In patients with Zollinger-Ellison syndrome the starting dose is 150 mg three times daily, increased as necessary up to a maximum of 6 grams daily.

In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients or the prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration, treatment with Ranitidine 150 mg twice daily may be substituted for ranitidine injection once oral feeding commences in patients considered to be still at risk from these conditions.

In obstetric patients an oral dose of 150 mg may be given at commencement of labour, followed by 150 mg at 6 hourly intervals. It is recommended that in addition, a non particulate antacid (e.g. sodium citrate) should be given prior to induction of anaesthesia in any patient requiring emergency general anaesthesia.

Children 12 years and over

For children 12 years and over the adult dosage is given.

Children from 3 to 11 years and over 30 kg of weight

Pharmacokinetic properties – Special Patient Populations

Peptic ulcer acute treatment

The recommended oral dose for the treatment of peptic ulcer in children is 4 mg/kg/day to 8 mg/kg/day administered as two divided doses to a maximum of 300 mg ranitidine per day for a duration of 4 weeks. For those patients with incomplete healing, another 4 weeks of therapy is indicated as healing usually occurs after eight weeks of treatment.

Gastro-oesophageal reflux

The recommended oral dose for the treatment of gastro-oesophageal reflux in children is 5 mg/kg/day to 10 mg/kg/day administered as two divided doses to a maximum dose of 600 mg (the maximum dose is likely to apply to heavier children or adolescents with severe symptoms).

Neonates

Safety and efficacy in new-born patients has not been established.

Renal insufficiency

Accumulation of ranitidine with resulting elevated plasma concentrations will occur in patients with renal impairment (creatinine clearance less than 50 ml/min). It is recommended that the daily dose of ranitidine in such patients should be 150 mg.

4.4 Special warnings and precautions for use

The possibility of malignancy should be excluded before commencement of therapy in patients with gastric ulcer as treatment with ranitidine may mask symptoms of gastric carcinoma.

In keeping with the recommended clinical practice, it is advisable that patients on long-term maintenance therapy receive regular routine assessments by their practitioners.

Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks. Ranitidine should, therefore, be avoided in patients with a history of acute porphyria.

Ranitidine is excreted via the kidney and so plasma levels of the active substance are increased in patients with renal impairment. The dose should be adjusted as detailed above in renal impairment.

In patients such as the elderly, persons with chronic lung disease, diabetes or the immunocompromised, there may be an increased risk of developing community acquired pneumonia. A large epidemiological study showed an increased risk of developing community acquired pneumonia in current users of H2 receptor antagonist versus those who had stopped treatment, with an observed adjusted relative risk increase of 1.82 (95% CI 1.26 – 2.64).

Regular supervision of patients who are taking non-steroidal anti-inflammatory drugs concomitantly with ranitidine is recommended especially in the elderly and in those with a history of peptic ulcer.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Ranitidine has the potential to affect the absorption, metabolism or renal excretion of other medicinal products. The altered pharmacokinetics may necessitate dosage adjustment of the affected medicinal product or discontinuation of treatment.

Interactions occur by several mechanisms including:

1) Inhibition of cytochrome P450-linked mixed function oxygenase system: Ranitidine at usual therapeutic doses does not potentiate the action of medicinal products which are inactivated by this enzyme system such as diazepam, lidocaine, phenytoin, propranolol and theophylline.

There have been reports of altered prothrombin time with coumarin anticoagulants (e.g. warfarin). Due to the narrow therapeutic index, close monitoring of increased or decreased prothrombin time is recommended during the concurrent treatment with ranitidine.

2) Competition for renal tubular secretion: Since ranitidine is partially eliminated by the cationic system, it may affect the clearance of other medicinal products eliminated by this route. High doses of ranitidine (e.g. such as those used in the treatment of Zollinger-Ellison syndrome) may reduce the excretion of procainamide and N-acetylprocainamide resulting in increased plasma levels of these medicinal products.

3) Alteration of gastric pH: The bioavailability of certain medicinal products may be affected. This can result in either an increase in absorption (e.g. triazolam, midazolam, glipizide) or a decrease in absorption (e.g. ketoconazole, atazanavir, delaviridine, gefitinib).

There is no evidence of an interaction between ranitidine, amoxicillin and metronidazole. If high doses (2 g) of sucralfate are co-administered with ranitidine the absorption of the latter may be reduced. This effect is not seen if sucralfate is taken after an interval of 2 hours.

4.6 Fertility, pregnancy and lactation

Fertility

There are no data on the effects of ranitidine on human fertility. There were no effects on male and female fertility in animal studies.

Pregnancy

Ranitidine crosses the placenta. Like other medicinal products ranitidine should only be used during pregnancy if considered essential.

Lactation

Ranitidine is excreted in human breast milk. Like other medicinal products ranitidine should only be used during breast-feeding if considered essential.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The following convention has been utilised for the classification of undesirable effects: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000) Not known (cannot be estimated from the available data).

Adverse event frequencies have been estimated from spontaneous reports from post-marketing data.

Blood & Lymphatic System Disorders

Very Rare: Blood count changes (leucopenia, thrombocytopenia). These are usually reversible. Agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or marrow aplasia.

Immune System Disorders Rare: Hypersensitivity reactions (urticaria, angioneurotic oedema, fever, bronchospasm, hypotension and chest pain)

These events have been reported after a single dose.

Psychiatric Disorders

Very Rare: Reversible mental confusion, depression and hallucinations.
These have been reported predominantly in severely ill, in elderly and in nephropathic patients.

Nervous System Disorders

Very Rare: Headache (sometimes severe), dizziness and reversible involuntary movement disorders.

Eye Disorders

Very Rare: Reversible blurred vision.

There have been reports of blurred vision, which is suggestive of a change in accommodation.

Cardiac Disorders

Very Rare:
As with other H2 receptor antagonists bradycardia, A-V Block and tachycardia.

Vascular Disorders

Very Rare: Vasculitis.

Gastrointestinal Disorders

Uncommon: Abdominal pain, constipation, nausea (these symptoms mostly improved during continued treatment)

Very Rare: Acute pancreatitis, diarrhoea.

Hepatobiliary Disorders

Rare: Transient and reversible changes in liver function tests

Very Rare: Hepatitis (hepatocellular, hepatocanalicular or mixed) with or without jaundice

Renal and Urinary Disorders

Rare: Elevation of plasma creatinine (usually slight; normalised during continued treatment)

Very rare: Acute interstitial nephritis.

Reproductive System and Breast Disorders

Very Rare: Reversible impotence, breast symptoms and breast conditions (such as gynaecomastia and galactorrhoea).

Paediatric population

The safety of ranitidine has been assessed in children aged 0 to 16 years with acid-related disease and was generally well tolerated with an adverse event profile resembling that in adults. There are limited long term safety data available, in particular regarding growth and development.

4.9 Overdose

Symptoms and Signs

Ranitidine is very specific in action and no particular problems are expected following overdose with ranitidine formulations.

Treatment

Symptomatic and supportive therapy should be given as appropriate. If need be, the drug may be removed from the plasma by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: H2 Antagonist

ATC Code: AO2BA02

Ranitidine is a specific, rapidly acting histamine H2-antagonist. It inhibits basal and stimulated secretion of gastric acid, reducing both the volume and the acid and pepsin content of the secretion. Ranitidine has a relatively long duration of action and so a single 150 mg dose effectively suppresses gastric acid secretion for twelve hours.

Although no clear casual link has been established, a large epidemiological study showed an increased risk of developing community acquired pneumonia in current users of H2 receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk increase of 1.63 (95% CI, 1.07 – 2.48).

5.2 Pharmacokinetic properties

Absorption: Following oral administration of 150 mg ranitidine, maximum plasma concentrations (300 to 550 ng/mL) occurred after 1-3 hours. Two distinct peaks or a plateau in the absorption phase result from reabsorption of drug excreted into the intestine. The absolute bioavailability of ranitidine is 50-60 %, and plasma concentrations increase proportionally with increasing dose up to 300 mg.

Distribution: Ranitidine is not extensively bound to plasma proteins (15 %), but exhibits a large volume of distribution ranging from 96 to 142 L.

Metabolism: Ranitidine is not extensively metabolised. The fraction of the dose recovered as metabolites is similar after both oral and i.v. dosing; and includes 6 % of the dose in urine as the N-oxide, 2 % as the S-oxide, 2 % as desmethylranitidine and 1 to 2 % as the furoic acid analogue.

Elimination: Plasma concentrations decline bi-exponentially, with a terminal half-life of 2-3 hours. The major route of elimination is renal. After i.v. administration of 150 mg 3H-ranitidine, 98 % of the dose was recovered, including 5 % in faeces and 93 % in urine, of which 70 % was unchanged parent drug. After oral administration of 150 mg 3H-ranitidine 96 % of the dose was recovered, 26 % in faeces and 70 % in urine of which 35 % was unchanged parent drug. Less than 3 % of the dose is excreted in bile. Renal clearance is approximately 500 mL/min, which exceeds glomerular filtration indicating net tubular secretion.

Special Patient Populations

Children (3 years and above)

Limited pharmacokinetic data have shown that there are no significant differences in half-life (range for children 3 years and above: 1.7 - 2.2 h) and plasma clearance (range for children 3 years and above: 9 - 22 ml/min/kg) between children and healthy adults receiving oral ranitidine when correction is made for body weight.

5.3 Preclinical safety data

Extensive studies have been carried out in animals. The pharmacology of ranitidine hydrochloride shows it to be a surmountable H2 receptor antagonist which produces an inhibition of gastric acid secretion.

Extensive toxicological investigations have been conducted which predicted a very safe profile for clinical use. This safety has since been confirmed by extensive use in patients for many years.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline Cellulose BP

Croscarmellose Sodium BP

Colloidal Anhydrous Silica BP

Magnesium Stearate BP

Purified Talc BP

Hypromellose E15 BP

Sunset Yellow FCF IH

6.2 Incompatibilities: Not Applicable

6.3 Shelf life: 24 months from the date of manufacturing.

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

10 Tablets are packed in an Aluminium strip. Such 10 Aluminium strips 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: