For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

ZINETAC 150 mg / 300 mg

1. GENERIC NAME

Ranitidine Tablets IP 150 mg / 300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZINETAC 150 mg

Each film- coated tablet contains:
Ranitidine Hydrochloride IP 168 mg equivalent to Ranitidine 150 mg
Colours: Sunset Yellow Lake, Titanium Dioxide IP

ZINETAC 300 mg

Each film -coated tablet contains:
Ranitidine Hydrochloride IP 336 mg equivalent to Ranitidine 300 mg
Colours: Sunset Yellow Lake, Lake Erythrosine, Titanium Dioxide IP

3. DOSAGE FORM AND STRENGTH

Film Coated Tablets

ZINETAC 150 mg

Each film- coated tablet contains:
Ranitidine Hydrochloride IP 168 mg equivalent to Ranitidine 150 mg
Colours: Sunset Yellow Lake, Titanium Dioxide IP

ZINETAC 300 mg

Each film- coated tablet contains:
Ranitidine Hydrochloride IP 336 mg equivalent to Ranitidine 300 mg
Colours: Sunset Yellow Lake, Lake Erythrosine, Titanium Dioxide IP

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Adults/Adolescents (12 years and over)

- Duodenal ulcer and benign gastric ulcer including that associated with non-steroidal anti-inflammatory agents.
- Prevention of non-steroidal anti-inflammatory drug (NSAID) (including aspirin) associated duodenal ulcers, especially in patients with a history of peptic ulcer disease.
- Duodenal ulcer associated with *Helicobacter pylori* infection.
- Post-operative ulcer.
- Reflux oesophagitis.

- Symptom relief in gastro-oesophageal reflux disease.
- Zollinger-Ellison syndrome.
- Prophylaxis of stress ulceration in seriously ill patients.
- Prophylaxis of recurrent haemorrhage from peptic ulcer.

4.2. Posology and Method of Administration

Adults/Adolescents (12 years and over)
Duodenal Ulcer and Benign Gastric Ulcer

- *Acute Treatment*

The standard dosage regimen for duodenal or benign gastric ulcer is 150 mg twice daily, or 300 mg once nightly. In most cases of duodenal ulcer or benign gastric 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 duodenal ulcer 300 mg twice daily for 4 weeks results in healing rates which are higher than those at 4 weeks with *ZINETAC* 150 mg twice daily or 300 mg once nightly. The increased dose has not been associated with an increased incidence of unwanted effects.

- *Long-Term Management*

For the long-term management of duodenal or benign gastric ulcer the usual dosage regimen is 150 mg once nightly.

Smoking is associated with a higher rate of duodenal 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 once nightly provides additional therapeutic benefit over the 150 mg dosage regimen.

NSAID Associated Peptic Ulceration

- *Acute Treatment*

In ulcers following non-steroidal anti-inflammatory drug therapy or associated with continued non-steroidal anti-inflammatory drugs, 8-12 weeks treatment may be necessary with 150 mg twice daily or 300 mg once nightly.

- *Prophylaxis*

For the prevention of non-steroidal anti-inflammatory drug associated duodenal ulcers *ZINETAC* 150 mg twice daily may be given concomitantly with non-steroidal anti-inflammatory drug therapy.

Duodenal Ulcer Associated with Helicobacter Pylori Infection

ZINETAC 300 mg once nightly or 150 mg twice daily may be given with oral amoxicillin 750 mg 3 times daily and metronidazole 500 mg 3 times daily for 2 weeks. Therapy with *ZINETAC* only should continue for a further 2 weeks. This dose regimen significantly reduces the frequency of duodenal ulcer recurrence.

Post-Operative Ulcer

The standard dosage regimen for post-operative ulcer is 150 mg twice daily. Most cases heal within 4 weeks. Those not fully healed after the initial 4 weeks usually do so after a further 4 weeks.

Gastro-Oesophageal Reflux Disease

- *Acute Treatment*

In reflux oesophagitis 150 mg twice daily or 300 mg once nightly is administered for up to a period of 8, or if necessary 12 weeks.

In patients with moderate to severe oesophagitis, the dosage of *ZINETAC* may be increased to 150 mg 4 times daily for up to 12 weeks.

- *Long-Term Management*

For the long-term management of reflux oesophagitis, the recommended adult oral dose is 150 mg twice daily.

- *Symptom Relief*

For the relief of symptoms associated with oesophageal acid reflux, the recommended regimen is 150 mg twice daily for 2 weeks. This regimen may be continued for a further 2 weeks in those patients in whom the initial response is inadequate.

Zollinger-Ellison Syndrome

The initial dosage regimen for Zollinger-Ellison syndrome is 150 mg 3 times daily, but this may be increased as necessary. Doses upto 6g per day have been well tolerated.

Prophylaxis of haemorrhage from stress ulceration in seriously ill patients or prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration

150 mg twice daily may be substituted for *ZINETAC* Injection once oral feeding commences.

Patients over 50 years of age

(*see Section 5.3 Pharmacokinetic Properties, 4.6 Use in Special Populations- Patients over 50 years of age*).

Renal Impairment

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 oral *ZINETAC* in such patients should be 150 mg.

4.3. Contraindications

ZINETAC products are contraindicated in patients known to have hypersensitivity to any component of the preparation.

4.4 Special Warnings and Precautions for Use

The possibility of malignancy should be excluded before commencement of therapy in patients with gastric ulcer and patients of middle age and over with new or recently changed dyspeptic symptoms, as treatment with *ZINETAC* may mask symptoms of gastric carcinoma.

Ranitidine is excreted via the kidney and so plasma levels of the drug are increased in patients with renal impairment. The dosage should be adjusted as detailed above under *Posology and Method of Administration* in *Renal Impairment*.

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

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

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 H_2 receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk increase of 1.63 (95% CI, 1.07 - 2.48).

4.5 Drug Interactions

Ranitidine has the potential to affect the absorption, metabolism or renal excretion of other drugs. The altered pharmacokinetics may necessitate dosage adjustment of the affected drug 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 actions of drugs 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 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 drugs 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 drugs.

3. Alteration of gastric pH

The bioavailability of certain drugs 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, gefitnib).

There is no evidence of an interaction between oral ranitidine and amoxicillin and metronidazole.

If high doses (2 g) of sucralfate are co-administered with oral 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 Use in Special Populations

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 (see *Section 6 Nonclinical Studies*).

Pregnancy and Lactation

Ranitidine crosses the placenta and is excreted in human breast milk. Like other drugs *ZINETAC* should only be used during pregnancy or during breast feeding if considered essential.

Patients over 50 years of age

In patients over 50 years of age, half-life is prolonged (3-4 h) and clearance is reduced, consistent with the age-related decline of renal function. However, systemic exposure and accumulation are 50% higher. This difference exceeds the effect of declining renal function and indicates increased bioavailability in older patients.

Renal Impairment

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 oral *ZINETAC* in such patients should be 150 mg.

4.7 Effects on Ability to Drive and Use Machines

None reported.

4.8 Undesirable Effects

The following convention has been utilised for the classification of undesirable effects:

very common	:	(≥1/10)
common	:	(≥1/100 to <1/10)
uncommon	:	(≥1/1000 to <1/100)
rare	:	(≥1/10,000 to <1/1000)
very rare	:	(<1/10,000)

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).
Very Rare: Anaphylactic shock.

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 and elderly 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 H_2 receptor antagonists bradycardia, A-V block

Vascular Disorders

Very Rare: Vasculitis.

Gastrointestinal Disorders

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, these were usually reversible.

Skin and Subcutaneous Tissue Disorders

Rare: Skin rash.
Very Rare: Erythema multiforme, alopecia.

Musculoskeletal and Connective Tissue Disorders

Very Rare: Musculoskeletal symptoms such as arthralgia and myalgia.

Renal and Urinary Disorders

Very rare: Acute interstitial nephritis.

Reproductive System and Breast Disorders

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

4.9 Overdose

ZINETAC is very specific in action and no problems are expected following overdose with *ZINETAC* formulations.
Symptomatic and supportive therapy should be given as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Ranitidine is a specific, rapidly acting histamine H_2-antagonist. It inhibits basal and stimulated secretion of gastric acid, reducing both the volume and the acid and pepsin content of the secretion.

5.2 Pharmacodynamic Effects

Ranitidine has a relatively long duration of action and so a single 150 mg oral dose effectively suppresses gastric acid secretion for 12 hours.

Clinical evidence has shown that oral ranitidine combined with amoxicillin and metronidazole eradicates *Helicobacter pylori* in approximately 90% of patients. This combination therapy has been shown to significantly reduce duodenal ulcer recurrence. *Helicobacter pylori* infects about 95% of patients with duodenal ulcer and 80% of patients with gastric ulcer.

5.3 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 after oral dosing includes 6% of the dose in urine as the N-oxide, 2% as the S-oxide, 2% as desmethyl ranitidine 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 oral administration of 150 mg ^{3}H-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 renal tubular secretion.

Special Patient Populations

Patients over 50 years of age

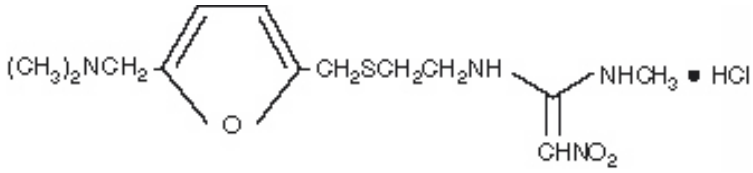
In patients over 50 years of age, half-life is prolonged (3-4 hours) and clearance is reduced, consistent with the age-related decline of renal function. However, systemic exposure and accumulation are 50% higher. This difference exceeds the effect of declining renal function, and indicates increased bioavailability in older patients.

6. NONCLINICAL PROPERTIES

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

7. DESCRIPTION

The active ingredient in ZINETAC 150 Tablets and ZINETAC 300 Tablets is ranitidine hydrochloride (HCl), USP, a histamine H2-receptor antagonist. Chemically it is N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, HCl. It has the following structure:



The empirical formula is $C_{13}H_{22}N_4O_3S$•HCl, representing a molecular weight of 350.87. Ranitidine HCl is a white to pale yellow granular substance that is soluble in water. It has a slightly bitter taste and sulfur-like odor.

List of Excipients

ZINETAC 150 mg

Microcrystalline Cellulose, Magnesium Stearate, Opadry II 85G53984 Orange (includes Sunset Yellow Lake and Titanium Dioxide).

ZINETAC 300 mg

Microcrystalline Cellulose, Crosscarmellose Sodium, Magnesium Stearate, Opadry II 85G530017 Orange (includes Sunset Yellow Lake, Lake Erythrosine, and Titanium Dioxide).

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

No data available.

8.2 Shelf Life

The expiry date is indicated on the label and packaging.

8.3 Nature and Specification of Container

Aluminium strips in a carton.

All presentations may not be marketed in the country.

8.4 Storage and Handling Information

Store at a temperature below 30°C, protected from light and moisture.

Keep out of reach of children.

There are no special requirements for use and handling of this product.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients about the Special Warnings and Precautions for Use, Drug Interactions, Undesirable Effects and any relevant contra-indications of *ZINETAC*. Patients may also be informed about Posology, Method of Administration and Storage/Handling Information as applicable.

10. DETAILS OF MANUFACTURER

The Manufacturing Site details are mentioned on the label and packaging.

For further information, please contact:
GlaxoSmithKline Pharmaceuticals Limited.
R**egistered Office**
Dr. Annie Besant Road, Worli,
Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Manufacturing License Number is indicated on the label and packaging.

12. DATE OF REVISION

11-FEB-2020

Version: ZIN-TAB/PI/IN/2020/01

Adapted from ZANTAC (Ranitidine Hydrochloride) GDS 46 dated 5 November 2018 / IPI 11 dated 27 November 2017.