PACKAGE INSERT TEMPLATE FOR RANITIDINE TABLET, RANITIDINE EFFERVESCENT TABLET, RANITIDINE EFFERVESCENT GRANULES & RANITIDINE SYRUP

Brand or Product Name
[Product name] Tablet 75mg
[Product name] Tablet 150mg
[Product name] Tablet 300mg
[Product name] Effervescent Tablet 150mg
[Product name] Effervescent Granules 150mg
[Product name] Syrup 15mg/ml

Name and Strength of Active Substance(s)
[Tablet]
Ranitidine hydrochloride ….mg equivalent to ranitidine 75mg
Ranitidine hydrochloride ….mg equivalent to ranitidine 150mg
Ranitidine hydrochloride ….mg equivalent to ranitidine 300mg

[Effervescent Tablet]
Ranitidine hydrochloride ….mg equivalent to ranitidine 150mg

[Effervescent Granules]
Ranitidine hydrochloride ….mg equivalent to ranitidine 150mg

[Syrup]
Ranitidine hydrochloride ….mg equivalent to ranitidine 15mg/ml

Product Description
[Visual description of the appearance of the product (eg colour, markings, flavour etc) eg :
Tablet - White, circular flat beveled edge film-coated tablets marked '150' on one side
Effervescent Tablet - White to pale yellow, round, flat, bevel-edged effervescent tablets. The tablet effervesces upon dissolution in water, to give a clear, orange flavoured solution.
Effervescent Granules – White, free-flowing granules
Syrup - Clear, orange-colored viscous syrup with the odor and flavor of oranges and sweet taste]

Pharmacodynamics
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.

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 h.

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.

Pharmacokinetics

Absorption

The bioavailability of oral ranitidine is consistently about 50%. Peak concentrations in plasma, normally in the range 300 to 550 nanograms/ml, occur 2 to 3 h after oral administration of a 150 mg dose. Concentrations of ranitidine in plasma are proportional to oral dose up to and including 300 mg.

Distribution

The volume of distribution ranges from 96 to 142 L. Serum protein binding averages 15%.

Metabolism

Ranitidine is not extensively metabolised. The metabolism of ranitidine is similar after both oral and i.v. dosing; about 6% of the dose being excreted in urine as the N-oxide, 2% as the S-oxide, 2% as desmethylranitidine and 1 to 2% as the furoic acid analogue.

Elimination

With 150 mg ^{3}H-ranitidine 60 to 70% of an oral dose was excreted in urine and 26% in faeces. Analysis of urine excreted in the first 24 h after dosing showed that 35% of the oral dose were eliminated unchanged. Elimination of the drug is primarily by tubular secretion. The elimination half-life is 2 to 3 h.

Indication

- 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.
- Duodenal ulcer associated with Helicobacter pylori infection.
- Post-operative ulcer.
- Reflux oesophagitis.
- Symptom relief in gastro-oesophageal reflux disease.
- Zollinger-Ellison Syndrome.
- Chronic episodic dyspepsia, characterised by pain (epigastric or retrosternal) which is related to meals or disturbs sleep but not associated with the above conditions.
- Prophylaxis of stress ulceration in seriously ill patients.
- Prophylaxis of recurrent haemorrhage from peptic ulcer.
- Prophylaxis of Mendelson's syndrome.

Recommended Dosage

Ranitidine effervescent tablets and ranitidine effervescent granules should be placed in half a glass of water (minimum 75 ml) and allowed to dissolve completely before swallowing, swirl the glass if necessary. For 300 mg doses a volume of 150 ml is recommended.

Adults

Duodenal ulcer and benign gastric ulcer

i) Acute treatment

The standard dosage regimen for duodenal or benign gastric ulcer is 150 mg twice daily or 300 mg nocte. In most cases of duodenal ulcer or benign gastric ulcer healing occurs within four weeks. Healing usually occurs after a further four weeks in those not fully healed after the initial four weeks. In duodenal ulcer 300 mg twice daily for four weeks results in healing rates which are higher than those at four weeks with Ranitidine 150 mg twice daily or 300 mg *nocte*. The increased dose has not been associated with an increased incidence of unwanted effects.

ii) Long-term management
For the long-term management of duodenal or benign gastric ulcer the usual dosage regimen is 150 mg *nocte*.
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 *nocte* provides additional therapeutic benefit over the 150 mg dosage regimen.

NSAID associated peptic ulceration
i) Acute treatment
In ulcers following non-steroidal anti-inflammatory drug therapy, or associated with continued non-steroidal anti-inflammatory drugs, 8 to 12 weeks treatment may be necessary with 150 mg twice daily or 300 mg *nocte*.

ii) Prophylaxis
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.

Duodenal ulcer associated with helicobacter pylori infection
Ranitidine 300 mg at bedtime or 150 mg twice daily may be given with oral amoxicillin 750 mg three times daily and metronidazole 500 mg three times daily for two weeks. Therapy with ranitidine only should continue for a further two 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 four weeks. Those not fully healed after the initial four weeks usually do so after a further four weeks.

Gastro-oesophageal reflux disease
i) Acute treatment
In reflux oesophagitis 150 mg twice daily or 300 mg nocte is administered for up to a period of 8, or if necessary, 12 weeks.
In patients with moderate to severe oesophagitis, the dosage of ranitidine may be increased to 150 mg four times daily for up to 12 weeks.

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

iii) Symptom relief
For the relief of symptoms associated with oesophageal acid reflux, the recommended regimen is 150 mg twice daily for two weeks. This regimen may be continued for a further two 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 three times daily, but this may be increased as necessary. Doses up to 6 g per day have been well tolerated.

Chronic episodic dyspepsia
The standard dosage regimen for patients with chronic episodic dyspepsia is 150 mg twice daily for up to six weeks. Anyone not responding or relapsing shortly afterwards should be investigated.

Prophylaxis of mendelson's syndrome
150 mg 2 h before anaesthesia, and preferably 150 mg the previous evening. Alternatively, the injection is also available. In obstetric patients in labour 150 mg every 6 h, but if general anaesthesia is required it is recommended that a non-particulate antacid (e.g. sodium citrate) be given in addition.

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 the injection once oral feeding commences.

Children
The recommended oral dose for the treatment of peptic ulcer in children is 2 mg/kg to 4 mg/kg twice daily to a maximum of 300 mg ranitidine per day.

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

Mode of Administration
Oral

Contraindications
Contraindicated in patients known to have hypersensitivity to any component of the preparation.

Warnings and Precautions
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 ranitidine may mask symptoms of gastric carcinoma.

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

Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks. Ranitidine 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 ranitidine 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. There is an increased risk of developing community acquired pneumonia in current users of H_2 receptor antagonists.

Effects on Ability to Drive and Use Machines
None reported.

Interactions with Other Medicaments
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:
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.

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.

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 h.

Statement on Usage During Pregnancy and Lactation
Ranitidine crosses the placenta and is excreted in breast milk. Like other drugs ranitidine should only be used during pregnancy or during nursing if considered essential.

Adverse Effects / Undesirable Effects
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 and, with the injection only, asystole.

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).

Overdose and Treatment
Ranitidine is very specific in action and no particular problems are expected following overdosage with ranitidine formulations. Symptomatic and supportive therapy should be given as appropriate.

Incompatibilities
Dilution of ranitidine syrup with Syrup BP or sorbitol solution is not recommended as this may result in precipitation. Ranitidine syrup should not be diluted or admixed with other liquid preparations.

Storage Conditions
Store below ….°C

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]