Ranitidine

QUALITATIVE AND QUANTITATIVE COMPOSITION
For all presentations, ranitidine is present as the hydrochloride salt.

Syrup:
Ranitidine 150 mg in 10 ml.

Tablets:
Ranitidine 150 mg or 300 mg.

Effervescent Tablets:
Ranitidine 150 mg or 300 mg.

Effervescent Granules:
Ranitidine 150 mg or 300 mg per sachet.

Injection:
Ranitidine 50 mg in 2 ml aqueous solution (25 mg/ml) or 5 ml aqueous solution (10 mg/ml).

PHARMACEUTICAL FORM
Oral Formulations
Syrup.
Tablets: film-coated and effervescent.
Effervescent Granules.

Parenteral Formulation
Injection.

CLINICAL PARTICULARS
Indications
Oral formulations:
- 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.

Injection:
- Duodenal Ulcer.
- Benign Gastric Ulcer.
- Post-operative Ulcer.
- Reflux Oesophagitis.
- Zollinger-Ellison Syndrome.
- Prophylaxis of stress ulceration in seriously ill.
- Prophylaxis of recurrent haemorrhage from peptic ulcer.
- Prophylaxis of Mendelson’s syndrome.

Dosage and Administration
General Information:
ZANTAC effervescent tablets and 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.

ZANTAC effervescent tablets and granules contain aspartame.

Populations
• Adults

Oral Formulations:
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
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
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 ZANTAC may be increased to 150 mg four 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 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.

Injection:
ZANTAC Injection may be given as:-
- a slow (over 2 min) i.v. injection of 50 mg, diluted to a volume of 20 ml, every 6 to 8 h.
- an intermittent i.v. infusion at 25 mg/h for 2 h, repeated at 6 to 8 h intervals.
- an i.m. injection of 50 mg every 6 to 8 h.

PROPHYLAXIS OF MENDELSON’S SYNDROME
For prophylaxis of Mendelson’s syndrome 50 mg by i.m. or slow i.v. injection 45 to 60 mins before induction of general anaesthesia.

PROPHYLAXIS OF HAEMORRHAGE FROM STRESS ULCERATION in seriously ill patients or prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration
In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients or prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration parenteral administration may be continued until oral feeding commences. Patients considered to be still at risk may then be treated with ZANTAC tablets 150 mg twice daily.

In the prophylaxis of upper gastrointestinal haemorrhage from stress ulceration in seriously ill patients a priming dose of 50 mg as a slow intravenous injection followed by a continuous intravenous infusion of 0.125-0.250 mg/kg/h may be preferred.

• 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 ZANTAC per day. Use of ZANTAC injection in children has not been evaluated.

• 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 ZANTAC in such patients should be 150 mg, and that ZANTAC injection be administered in doses of 25 mg.

Contraindications
ZANTAC products are 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 ZANTAC 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 Dosage and Administration in Renal Impairment.

Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks.

ZANTAC 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 ZANTAC 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 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).
As ZANTAC effervescent tablets and granules contain aspartame they should be used with caution in patients with phenylketonuria.

ZANTAC effervescent tablets and granules contain sodium (see List of Excipients for sodium content). Care should therefore be taken in treating patients in whom sodium restriction is indicated.

Bradycardia in association with rapid administration of ZANTAC injection has been reported rarely, usually in patients with factors predisposing to cardiac rhythm disturbances. Recommended rates of administration should not be exceeded.

The use of higher than recommended doses of i.v. H 2- antagonists has been associated with rises in liver enzymes when treatment has been extended beyond five days.

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, delavirdine, gefitinib).

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

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

Effects on Ability to Drive and Use Machines
None reported.

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

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<thead>
<tr>
<th>Frequency</th>
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<tr>
<td>very common:</td>
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<td>common:</td>
</tr>
<tr>
<td>uncommon:</td>
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<tr>
<td>rare:</td>
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<tr>
<td>very rare:</td>
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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 H2 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 in men.

Overdose
Ranitidine is very specific in action and no particular problems are expected following overdosage with ZANTAC formulations. Symptomatic and supportive therapy should be given as appropriate.
Clinicians should be aware of the sodium content of ZANTAC effervescent tablets and granules (see List of Excipients).

Pharmacodynamics
Mechanism of Action
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.

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 amoxycillin 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.
Absorption of ranitidine after i.m. injection is rapid and peak plasma concentrations are usually achieved within 15 min of administration.

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 desmethyl-ranitidine and 1 to 2% as the furoic acid analogue.
Elimination
In balance studies with 150 mg 3H-ranitidine 93% of an i.v. dose was excreted in urine and 5% in faeces; 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 70% of the i.v. dose and 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.

Pre-clinical Safety Data
No additional data of relevance

PHARMACEUTICAL PARTICULARS
List of Excipients
Syrup:
Hydroxypropyl methylcellulose 2906 or 2910 (4000 cP)
Ethanol (96 percent)
Propyl hydroxybenzoate
Butyl hydroxybenzoate
Potassium dihydrogen orthophosphate
Disodium hydrogen orthophosphate anhydrous
Sodium chloride
Saccharin sodium
Sorbitol 70 per cent (Non-crystallising)
Mint flavour IFF 17:42:3632
Purified water

Tablets:
Tablet core:
Microcrystalline cellulose
Crocarmellose sodium (300 mg tablet only)
Magnesium stearate

Film coat:
Opadry white OY-S-7322
Purified water

Effervescent Tablets:
Monosodium citrate anhydrous
Sodium hydrogen carbonate
Aspartame
Povidone K30
Sodium benzoate

Injection:
25 mg/ml:
Disodium hydrogen orthophosphate
Sodium Chloride
Potassium dihydrogen orthophosphate anhydrous
Water for injections
Nitrogen.

10 mg/ml:
Water for injections.

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

For Injection information, see Instructions for Use/ Handling.

Shelf Life
The expiry date is indicated on the packaging.

Special Precautions for Storage
ZANTAC syrup should be stored below 25oC.
ZANTAC film-coated tablets, effervescent tablets and granules should be stored at a temperature below 30oC.

Injection:
Protect from light
ZANTAC injection should not be autoclaved.
Store below 25oC.

**Nature and Contents of Container**

**Syrup:**
Amber glass bottle (hydrolytic class III) with child resistant cap.

**Tablets:**
The tablets are packed either in foil strips or double foil blisters.

**Effervescent Granules:**
Heat sealed laminate of paper/aluminium foil/polyethylene.

**Effervescent Tablets:**
The tablets are packed either in foil strips or double foil blisters.

**Injection:**
Clear type 1 glass ampoules.

**Instructions for Use/Handling**
ZANTAC injection is compatible with the following i.v. infusion fluids:-
- 0.9% sodium chloride
- 5% dextrose
- 0.18% sodium chloride and 4% dextrose
- 4.2% sodium bicarbonate
- Hartmann’s solution.

Unused admixtures should be discarded 24 h after preparation.

Although compatibility studies have only been undertaken in polyvinyl chloride infusion bags (in glass for sodium bicarbonate) and polyvinyl chloride administration sets, it is considered that adequate stability would be conferred by the use of a polyethylene infusion bag.

Not all presentations are available in every country.

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ZANTAC is a trademark of the GlaxoSmithKline group of companies