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Zantac™ Injection 25 mg/ml

TITLE

Ranitidine hydrochloride.

SCOPE

Trade Name

ZANTAC™ Injection 25mg/ml

Formulation and Strength

Ranitidine Hydrochloride 56.0 mg/2 ml equivalent to ranitidine 50.0 mg/ 2 ml.

Injection (Aqueous solution)

Excipients

Sodium Chloride
Potassium Dihydrogen Orthophosphate
Disodium Hydrogen Orthophosphate Anhydrous
Water for Injection

Each ml also contains : approx. 0.84 mg Sodium.

CLINICAL INFORMATION

Indications

- ***Adults/Adolescents (12 years and over)***

Ranitidine Injection is indicated for the treatment of:

- Duodenal ulcer
- Benign gastric ulcer
- Post-operative ulcer
- Reflux oesophagitis
- Zollinger-Ellison Syndrome
- Before general anaesthesia in patients considered to be at risk of acid aspiration (Mendelson's Syndrome)

- Prophylaxis of stress ulceration in seriously ill patients.
For appropriate cases, Ranitidine tablets are also available.

Dosage and Administration

Populations

- **Adults**

Ranitidine Injection may be given as**:**
- a slow (over a period of at least two minutes) intravenous injection of 50 mg, after dilution to a volume of 20 ml per 50 mg dose, which may be repeated every six to eight hours;
- an intermittent intravenous infusion at a rate of 25 mg per hour for two hours; the infusion may be repeated at six to eight hour intervals
- an i.m. injection of 50 mg (2 ml) every six to eight hours.

PROPHYLAXIS OF MENDELSON'S SYNDROME

For prophylaxis of Mendelson's syndrome 50 mg may be given intramuscularly or by slow intravenous injection 45 to 60 minutes before induction of general anaesthesia.

PROPHYLAXIS OF HAEMORRHAGE FROM STRESS ULCERATION IN SERIOUSLY ILL PATIENTS
In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients parenteral administration may be continued until oral feeding commences. Patients considered to be still at risk may then be treated with Ranitidine 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 continuous intravenous infusion of 0.125-0.250 mg/kg/hr may be preferred.

- **Children**

The use of Ranitidine Injection in children has not been evaluated.
Safety and efficacy in neonates has not been established.

- **Patients over 50 years of age**

See Pharmacokinetics, Special Patient 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 in such patients that ranitidine be administered in doses of 25 mg.
Route of Administration- Intravenous or intramuscular injection.

Contraindications

- Ranitidine is contraindicated for patients known to have hypersensitivity to any component of the preparation.

Warnings and Precautions

Treatment with a histamine H_2-antagonist may mask the symptoms associated with carcinoma of the stomach and may therefore delay diagnosis of the condition. Accordingly, where gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with Zantac is instituted.

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 Dosage and Administration 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.

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 1.82 (95% CI 1.26-2.64). Postmarketing data indicate reversible mental confusion, depression, and hallucinations have been reported most frequently in severely ill and elderly patients (see section Adverse Reactions).

Bradycardia in association with rapid administration of Ranitidine 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 intravenous H_2-antagonist 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, delaviridine, gefitnib).

Pregnancy and Lactation

Pregnancy

Ranitidine crosses the placenta but therapeutic doses administered to obstetric patients in labour or undergoing caesarean section have been without any adverse effect on labour, delivery or subsequent neonatal progress. . Like other drugs, Ranitidine should only be used during pregnancy if considered essential.

Lactation

Ranitidine is excreted in human breast milk. Like other drugs, Ranitidine should only be used during nursing if considered essential.

Ability to perform tasks that require judgement, motor or cognitive skills

None reported.

Adverse Reactions

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).
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 asystole.

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, 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

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)

Overdosage

Symptoms and Signs

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

Treatment

Symptomatic and supportive therapy should be given as appropriate.

Clinical Pharmacology

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.

Pharmacokinetics

Absorption

Absorption of ranitidine after intramuscular injection is rapid and peak plasma concentrations are usually achieved within 15 minutes of administration.

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 the urine as the N-oxide, 2% as the S-oxide, 2% as desmethylranitidine and 1-2% 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 IV 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 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 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.

NON-CLINICAL INFORMATION

No additional data of relevance.

PHARMACEUTICAL INFORMATION

Shelf life

36 moths unopened
All unused admixtures of Ranitidine Injection with infusion fluids should be discarded 24 hours after preparation.

Storage

Store below 25°C,
Protect from light.
Ranitidine Injection should not be autoclaved.

Nature and contents of container

2 ml colourless Type I glass ampoules. Pack size: 5 ampoules.

Incompatibilities

(See Use and Handling).

Use and Handling

Ranitidine injection is a clear, colourless to pale yellow liquid.

Ranitidine injection is compatible with the following i.v. infusion fluids:-

- 0.9% Sodium Chloride BP.
- 5% Dextrose BP.
- 0.18% Sodium Chloride and 4% Dextrose BP.
- 4.2% Sodium Bicarbonate BP.
- 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 BP) and polyvinyl chloride administration sets it is considered that adequate stability would be conferred by the use of a polyethylene infusion bag.

Manufacturer: GlaxoSmithKline Manufacturing SPA, Parma, Italy

License Holder and Importer: GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva

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