PACKAGE INSERT TEMPLATE FOR RANITIDINE SOLUTION FOR INTRAVENOUS AND INTRAMUSCULAR INJECTION

Brand or Product Name
[Product name] Solution for IV/IM Injection

Name and Strength of Active Substance(s)
Ranitidine hydrochloride ….mg equivalent to ranitidine 25mg/ml

Product Description
[Visual description of the appearance of the product (eg colour, odour etc)
eg :A clear colorless sterile liquid]

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

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 93% of an i.v. dose was excreted in urine and 5% in faeces. Analysis of urine excreted in the first 24 h after dosing showed that 70% of the i.v. 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.
- 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.

Recommended Dosage
Ranitidine 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 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 a continuous intravenous infusion of 0.125-0.250 mg/kg/h may be preferred.

Children
Use of ranitidine 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). Ranitidine injection is recommended to be administered in doses of 25 mg.

Mode of Administration
Intravenous injection (slow IV injection and intermittent IV infusion)
Intramuscular injection

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.

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- antagonists has been associated with rises in liver enzymes when treatment has been extended beyond five days.

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).

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

Instruction for Use
Ranitidine Injection has been shown to be compatible with the following intravenous 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.

Storage Conditions
Finished product - Store below ….°C
Admixtures of Ranitidine Injection with infusion fluids - Store below ….°C for ….hours.
* If not, please include this statement - For single use only. Discard any unused portion after preparation.

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]