Ranitidine Injection USP 25mg/1ml, 50mg/2ml, 150mg/6ml

1. Name of the medicinal product

Ranitidine Injection USP 25mg/1ml Taj Pharma

Ranitidine Injection USP 50mg/2ml Taj Pharma

Ranitidine Injection USP 150mg/6ml Taj Pharma

2. Qualitative and quantitative composition

a)Ranitidine Injection USP 25mg/1ml Taj Pharma
Each ml contains:
Ranitidine as Ranitidine hydrochloride
is equivalent to 25mg
Phenol 5mg
Dibasic Potassium phosphate as buffer

b)Ranitidine Injection USP 50mg/2ml Taj Pharma
Each ml contains:
Ranitidine as Ranitidine hydrochloride
is equivalent to 25mg
Phenol 5mg
Dibasic Potassium phosphate as buffer

c)Ranitidine Injection USP 150mg/6ml Taj Pharma
Each ml contains:
Ranitidine as Ranitidine hydrochloride
is equivalent to 25mg
Phenol 5mg
Dibasic Potassium phosphate as buffer

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Injection

Colourless to almost colourless clear liquid.

4. Clinical particulars

4.1 Therapeutic indications

Ranitidine Injection is indicated in treatment benign gastric and duodenal ulceration including reflux oesophagitis, post operative ulcers and other conditions where reduction of gastric acid output is beneficial: prophylaxis of gastrointestinal haemorrhage from stress ulceration in seriously ill patients, the prophylaxis of recurrent haemorrhage in patients with bleeding peptic ulcers and in patients before general anaesthesia considered to be at risk of acid aspiration (Mendelson's Syndrome), particularly obstetric patients during labour. Ranitidine is also indicated in Zollinger – Ellison Syndrome

Paediatric population (6 months to 18 years)

- Short term treatment of peptic ulcer

- Treatment of gastro-oesophageal reflux, including reflux oesophagitis and symptomatic relief of gastro-oesophageal reflux disease.

4.2 Posology and method of administration

Posology

Adults (including older people) / Adolescents (12 years and over)

Ranitidine Solution for Injection may be given at a dose of 50mg either as slow intravenous injection, intermittent intravenous infusion or intramuscularly.

Slow intravenous injection:

50mg diluted to a volume of 20ml and given over at least a period of 2 minutes which may be repeated every 6 to 8 hours.

Intermittent intravenous infusion:

25mg per hour for 2 hours; may be repeated 6 to 8 hours.

Intramuscular injection:

50mg (2ml) every six to eight hours.

Parenteral administration for the prophylaxis of haemorrhage from stress ulceration in seriously ill patients or the prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration may be continued until oral feedings commences. Patients considered at risk requiring

further treatment may then be transferred to treatment with ranitidine tablets.

For prophylaxis of upper gastro-intestinal haemorrhage from stress ulceration in seriously ill patients it may be preferable to give a priming dose of 50mg by slow intravenous injection followed by a continuous intravenous infusion of 0.125 – 0.25mg/kg/hr.

In patients considered to be at risk of developing acid aspiration syndrome, ranitidine 50mg may be given 45-60 minutes before induction of general anaesthesia either intramuscularly or by slow intravenous injection (over at least 2 minutes).

Older people

Normal dosage (as per adults) is recommended except in patients who have moderate to severe renal impairment.

Paediatric population

Children/infants (6 months to 11 years):

See Section 5.2 Pharmacokinetic Properties - Special Patient Populations.

Ranitidine Injection may be given as a slow (over 2 minutes) i.v. injection up to a maximum of 50mg every 6 to 8 hours.

Neonates (under 1 month)

See Section 5.2. Pharmacokinetic Properties – Special Patient Populations.

Peptic Ulcer Acute Treatment and Gastro-Oesophageal Reflux

Intravenous therapy in children with peptic ulcer disease is indicated only when oral therapy is not possible.

For acute treatment of peptic ulcer disease and gastro-oesophageal reflux in paediatric patients, Ranitidine injection may be administered at doses that have been shown to be effective for these diseases in adults and effective for acid suppression in critically ill children. The initial dose (2.0 mg/kg or 2.5 mg/kg, maximum 50 mg) may be administered as a slow intravenous infusion over 10 minutes, either with a syringe pump followed by a 3 mL flush with normal saline over 5 min, or following dilution with normal saline to 20 mL. Maintenance of pH > 4.0 can be achieved by intermittent infusion of 1.5 mg/kg every 6 h to 8 h. Alternatively treatment can be continuous, administering a loading dose of 0.45 mg/kg followed by a continuous infusion of 0.15 mg/kg/hr.

Prophylaxis of stress ulceration in seriously ill patients

The recommended dose for prophylaxis of stress ulceration is 1mg/kg (maximum 50 mg) every 6h to 8h.

Alternatively treatment can be continuous, administering 125 - 250 micrograms/kg/hr as continuous infusion.

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). Accordingly, it is recommended in such patients that ranitidine be administered in doses of 25 mg.

Method of administration

Intravenous or intramuscular injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Treatment with a histamine H2 antagonist may mask the symptoms associated with carcinoma of the stomach and may therefore delay diagnosis of the condition. Where gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with Ranitidine Solution for injection is started.

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 in section 4.2.

Bradycardia in association with rapid administration of Ranitidine Solution for

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

It has been reported that 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.

Although clinical reports of acute intermittent porphyria associated with ranitidine administration have been rare and inconclusive, ranitidine should be avoided in patients with a history of this condition.

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 1.82 (95% CI 1,26 - 2,64).

Post marketing data indicate reversible mental confusion, depression, and hallucinations have been reported most frequently in severely ill and elderly patients (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

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).

4.6 Fertility, 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 by a physician.

Breast-feeding

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

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.

4.7 Effects on ability to drive and use machines

Ranitidine Injection has no or negligible influence on the ability to drive and use machines.

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 (≥1/1,000 to <1/100); rare (≥1/10,000 to <1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Adverse event frequencies have been estimated from spontaneous reports from postmarketing 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 (injection only).

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)

Paediatric population

The safety of ranitidine has been assessed in children aged 0 to 16 years with acid-related disease and was generally well tolerated with an adverse event profile resembling that in adults. There are limited long term safety data

available, in particular regarding growth and development.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important.

4.9 Overdose
Symptoms

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

Management

Symptomatic and supportive therapy should be given as appropriate. Ranitidine may be removed by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: H_2 receptor antagonists

Mechanism of action

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

The clinical data available mentions the use of ranitidine in children to prevent stress ulcers. No direct evidence for prevention of stress ulcers is available. Treatment for these patients is based on the observation that pH is above 4 after administration of ranitidine. The value of this surrogate parameter in children with stress ulcers remains to be established.

5.2 Pharmacokinetic properties
Absorption

Peak plasma concentration is rapid and usually achieved within 15 minutes following intramuscular injection.

Distribution

Rantidine is not extensively bound to plasma proteins (15%), but exhibits a large volume of distribution ranging from 96 to 142 L.

Biotransformation

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 urine as the N-oxide, 2% as the S-oxide, 2% as desmethylranitidine 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 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 500mL/min, which exceeds glomerular filtration indicating net renal tubular secretion.

Special Patient Populations

Children/infants (6 months and above)

Limited pharmacokinetic data show that there were no significant differences in half-life (range for children 3 years and above: 1.7 - 2.2 h) and plasma clearance (range for children 3 years and above: 9 - 22 ml/min/kg) between children and healthy adults receiving intravenous ranitidine when correction is made for body weight. Pharmacokinetic data in infants is extremely limited but appears to be in line with that for older children.

Patients over 50 years of age

In patients over 50 years of age, half life is prolonged (3-4h) 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.

Paediatric population

Neonates (under 1 month)

Limited pharmacokinetic data from term babies undergoing treatment with Extracorporeal Membrane Oxygenation (EMCO) suggests that plasma clearance following iv administration may be reduced (1.5-8.2 ml/min/kg) and the half-life increased in the new-born. Clearance of ranitidine appeared to be related to the estimated glomerular filtration rate in the neonates.

5.3 Preclinical safety data
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.

6. Pharmaceutical particulars

6.1 List of excipients
Sodium chloride

Monopotassium phosphate

Anhydrous disodium phosphate

Water for Injection

Nitrogen

6.2 Incompatibilities
Ranitidine 50mg in 2 ml solution for injection should not be mixed with any other medicinal products.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 25°C. Do not freeze.

Keep the container in the outer carton in order to protect from light.

6.5 Nature and contents of container
Type I clear glass ampoules

Pack size: 2ml x 5 ampoules

6.6 Special precautions for disposal and other handling
Ranitidine 50mg/2ml Solution for injection may be diluted with Sodium Chloride intravenous infusion (0.9%). If stored incorrectly discolouration of the solution may occur.

Injection should not be autoclaved.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7.Manufactured in India by:
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