

## **1. NAME OF THE MEDICINAL PRODUCT**

Ranitidine 50mg in 2ml Injection

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Ranitidine (as hydrochloride) 50mg in 2ml

For excipients see 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

#### Children (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**

#### Adults (including elderly) / Adolescents (12 years and over)

Ranitidine 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)

The elderly:

Normal dosage is recommended except in patients who have moderate to severe renal impairment

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.

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.

Neonates (under 1 month)

See Section 5.2 Pharmacokinetic Properties – Special Patient Populations.

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.

Route of Administration

Intravenous or intramuscular injection

#### **4.3. Contraindications**

Ranitidine is contraindicated for patients known to have hypersensitivity to ranitidine, H<sub>2</sub> – receptor antagonists or any of the other ingredients of the preparation.

#### **4.4 Special warnings and precautions for use**

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 i.v. H<sub>2</sub>- antagonists has been associated with rises in liver enzymes when treatment has been extended beyond five days.

The possibility of malignancy should be excluded before commencement of therapy in patients with gastric ulcer [and if indications include dyspepsia; patients of middle age and over with new or recently changed dyspeptic symptoms must be included] 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 Dosage and Administration in Section 4.2 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 ranitidine alone H<sub>2</sub> receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk increase of 1,82 (95% CI 1,26- 2,64).

#### **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, gefitinib).

#### **4.6 Pregnancy and lactation**

Pregnancy

Ranitidine crosses the placenta.

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.

#### **4.7 Effects on ability to drive and use machines**

None reported.

#### **4.8 Undesirable effects**

The following convention has been utilised for the classification of undesirable effects:  
very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1,000$ ); very rare ( $< 1/10,000$ ).

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 H<sub>2</sub> receptor antagonists bradycardia, A-V block and asystole (injection only).

#### Vascular Disorders

Very Rare: Vasculitis.

#### Gastrointestinal Disorders

Very Rare: Acute pancreatitis

Uncommon: abdominal pain, diarrhoea, constipation, nausea (these symptoms mostly improved during continued treatment).

#### 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.

## 4.9 Overdose

### Symptoms and Signs

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

### Treatment

No specific antidote is available. If necessary the drug can be removed by haemodialysis. Symptomatic and supportive therapy should be given as appropriate.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

H<sub>2</sub> receptor antagonists, A02BA

Ranitidine is a selective, rapidly acting histamine H<sub>2</sub>-antagonist which rapidly inhibits both basal and stimulated gastric secretion of acid and reduces pepsin output.

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

Peak plasma concentration is rapid and usually achieved within 15 minutes following intramuscular injection. Ranitidine is not extensively metabolised with elimination of the drug primarily by tubular secretion. The elimination half-life is approximately 2-3 hours.

Published data shows that in balance, studies using 150mg 3H-ranitidine; 93% of an intravenous dose was excreted in urine and 5% in faeces. Analysis of urine excreted in the first 24 hours after dosing showed that 70% of the intravenous dose was eliminated

unchanged. About 6% of the dose is excreted in the urine as the N-oxide, 2% as desmethyl ranitidine and 1-2% as the furoic acid analogue.

### 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.

#### 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 newborn. Clearance of ranitidine appeared to be related to the estimated glomerular filtration rate in the neonates.

### **5.3. Preclinical safety data**

There was no indication of tumorigenic or carcinogenic effects in life-span studies in mice and rats at dosages up to 2,000 mg/kg per day.

Ranitidine was not mutagenic in standard bacterial tests (Salmonella, Escherichia coli) for mutagenicity at concentrations up to the maximum recommended for these assays. In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

## **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. Instruction for use and handling (, and disposal)**

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 solution must be discarded.

No Data Held

**7. MARKETING AUTHORISATION HOLDER**

Antigen International Limited,  
Roscrea,  
Co Tipperary,  
Republic of Ireland

**8. MARKETING AUTHORISATION NUMBER**

PL 02848/0213

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

5<sup>th</sup> January 2005

**10      DATE OF REVISION OF THE TEXT**

01/07/2010