Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zantac 25 mg/ml Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains ranitidine hydrochloride equivalent to 50 mg ranitidine in 2 ml i.e. 25 mg/ml.

Each ampoule also contains 2.9 mg (0.09 mmol) of sodium and 0.6 mg (0.015 mmol) of potassium.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection/Infusion.

A sterile, clear colourless to pale yellow aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Zantac is used in the treatment of benign ulceration of the oesophagus, stomach, upper intestinal tract (including post-operative stomal area), and of the Zollinger-Ellison syndrome.

In the management of conditions benefiting from reduced gastric acid secretion, such as reflux oesophagitis.

As prophylaxis against:
(i) acid aspiration (Mendelson's) syndrome
(ii) stress lesions of the upper gastrointestinal tract.
(iii) recurrent haemorrhage from the upper gastrointestinal tract.

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

Posology

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

Zantac Injection may be given either as a slow (over 2 minutes) intravenous injection of 50 mg, diluted to a volume of 20 ml, every six to eight hours as required until oral therapy can be introduced; or as an intermittent intravenous infusion at 25 mg per hour for two hours, repeated at six to eight hour intervals; or as an intramuscular injection of 50 mg every six to eight hours.

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 the continuous intravenous infusion of 0.125-0.250 mg/kg/hr may be preferred.

In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients or the 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 patients considered to be at risk of developing acid aspiration (Mendelson's) syndrome, Zantac Injection 50 mg may be given intramuscularly or by slow intravenous injection 45 to 60 minutes before induction of general anaesthesia.

Children / Infants (6 months to 11 years)

See section 5.2 Pharmacokinetic properties – Special Patient Populations.

Zantac injection may be given as a slow (over 2 minutes) i.v. injection up to a maximum of 50 mg 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, Zantac injection may be administered at doses that have been shown to be effective for 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.

Neonates (under 1 month)
See section 5.2 Pharmacokinetic Properties – Special Patient Populations

Patients with renal impairment
Accumulation of ranitidine with resulting elevated plasma concentrations will occur in patients with severe renal impairment (creatinine clearance less than 50ml/min). It is recommended in such patients that Zantac be administered in doses of 25mg.

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

Asystole and 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 intravenous H_2-antagonist 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 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 renal impairment. The dosage should be adjusted as detailed in Section 4.2.

Rare clinical reports suggest that ranitidine may precipitate acute porphric 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 versus those who had stopped treatment, with an observed adjusted relative risk increase of 1.82 (95% CI 1.26 – 2.64).

This medicine contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially 'sodium-free'.

This medicine contains potassium, less than 1 mmol (39 mg) per ampoule, i.e. essentially 'potassium-free'.

4.5 Interaction with other medicinal products and other forms of 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).

Concomitant administration of 300 mg ranitidine and erlotinib decreased erlotinib exposure [AUC] and maximum concentrations [C_{max}] by 33% and 54%, respectively. However, when erlotinib was dosed in a staggered manner 2 hours before or 10 hours after ranitidine 150 mg b.i.d., erlotinib exposure [AUC] and maximum concentrations [C_{max}] decreased only by 15% and 17%, respectively.

There is no evidence of an interaction between ranitidine and amoxicillin and metronidazole. If high doses (2 g) of sucralfate are co-administered with ranitidine the absorption of the latter may be reduced. This effect is not seen if sucralfate is taken after an interval of 2 hours.

4.6 Fertility, pregnancy and lactation

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.

Pregnancy
Ranitidine crosses the placenta. Like other drugs ranitidine should only be used during pregnancy if considered essential.

Breast-feeding
Ranitidine is excreted in human breast milk. Like other drugs ranitidine should only be used during breast-feeding 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 (>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
Unknown: Dyspnoea

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, in elderly and in nephropatic 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, tachycardia and asystole.

Vascular Disorders
Very Rare: Vasculitis.

Gastrointestinal Disorders
Very Rare: Acute pancreatitis. Diarrhoea.
Uncommon: Abdominal pain, 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
Very rare: Acute interstitial nephritis.
Rare: Elevation of plasma creatinine (usually slight; normalised during continued treatment).

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. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms and signs
Ranitidine is very specific in action and no particular problems are expected following overdosage with the drug.

Treatment
Symptomatic and supportive therapy should be given as appropriate. If need be, the drug may be removed from the plasma by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alimentary tract and metabolism.
ATC code: A02 BA02.

Mechanism of action

Zantac 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.

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:
Following oral administration of 150 mg ranitidine, maximum plasma concentrations (300 to 550 ng/mL) occurred after 1-3 hours. Two distinct peaks or a plateau in the absorption phase result from reabsorption of drug excreted into the intestine. The absolute bioavailability of ranitidine is 50-60 %, and plasma concentrations increase proportionally with increasing dose up to 300 mg.

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

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 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 i.v. administration of 150 mg ^{3}H-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 ^{3}H-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 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.

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

No additional data of relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Potassium Dihydrogen phosphate
Disodium phosphate Anhydrous
Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in *section 6.6*.

6.3 Shelf life

3 years

All admixtures of Zantac Injection with compatible infusion fluids (as listed in Section 6.6) should be stored below 25°C and discarded 24 hours after preparation.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. Dilution should take place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C. Keep ampoule in the outer carton in order to protect from light. Do not autoclave.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

Zantac Injection is 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.

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 use of a polyethylene infusion bag.

For single use only. Discard any unused content.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1077/013/001

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