Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ranitidine 50 mg/2 ml Solution for Injection and Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each one ml of solution contains 25 mg ranitidine as ranitidine hydrochloride. Each 2 ml ampoule contains 50 mg ranitidine.

Excipient(s) with known effect:
Each ampoule contains 0.55 mg (0.014 mmol) of Potassium and 2.23 mg (0.097 mmol) of Sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection and Infusion

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults
Ranitidine Solution for Injection is indicated for the treatment of duodenal ulcer, benign gastric ulcer, post - operative ulcer, and of Zollinger - Ellison Syndrome.

In the management of conditions where reduction of gastric secretion and acid output is desirable, such as reflux oesphagitis.

As prophylaxis against:

- gastrointestinal haemorrhage from stress ulceration in seriously ill patients
- recurrent haemorrhage in patients with bleeding peptic ulcers
- acid aspiration (Mendelson's Syndrome) before anaesthesia in patients at risk, particularly obstetric patients during labour.

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

See section 5.2 Pharmacokinetic Properties – Special Patient Populations

Posology
Adults (including elderly) and adolescents (12 years and older)
Ranitidine Solution for Injection may be given as:

- a slow intravenous injection (over two minutes) up to a maximum of 50 mg, after dilution to a volume of 20 ml per 50 mg dose. This dose may be repeated every 6 to 8 hours or
- as an intermittent intravenous infusion at a rate of 25 mg per hour for two hours. The infusion may be repeated at 6 to 8 hour intervals
- as an intramuscular injection of 50 mg (2 ml) every 6 to 8 hours.

Prophylaxis of haemorrhage from stress ulceration or recurrent haemorrhage:
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 orally with Ranitidine tablets 150 mg twice daily.

In the prophylaxis of upper gastro-intestinal 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/hr may be preferred.

Prophylaxis of Mendelson's syndrome:
In patients considered at risk of developing acid aspiration (Mendelson's) syndrome, Ranitidine Solution for Injection 50 mg may be given intramuscularly or by slow intravenous injection, 45 to 60 minutes before induction of general anaesthesia.
Children / Infant (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 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, 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.

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

Patients over 50 years of age
See Section 5.2 Pharmacokinetic properties (Special Patient Populations, Patients over 50 years of age).

Patients with 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.

Method of Administration
Intravenous or intramuscular injection

For instructions on dilution of the medicinal product before administration, see section 6.6

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Malignancy
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

Renal Disease
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 Patients with Renal Impairment.

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.

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.

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 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 Undesirable effects).

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 systems 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 (such as those used in the treatment of Zollinger-Ellison syndrome) may reduce the excretion of procainamide and N-acetylprocainamide resulting in increased plasma level 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) Erlotinib and medicinal products altering pH
Concomitant administration of 300mg ranitidine and erlotinib decreased erlotinib exposure [AUC] and maximum concentrations [Cmax] by 33% and 54%, respectively. However, when erlotinib was dosed in a staggered manner 2 hours before or 10 hours after ranitidine 150mg b.i.d., erlotinib exposure [AUC] and maximum concentrations [Cmax] decreased only by 15% and 17%, respectively.

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.

Breast-feeding
Ranitidine is also excreted in human breast milk. Like other drugs, ranitidine should only be used during breast-feeding 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 (see section 5.3).

4.7 Effects on ability to drive and use machines

None known.

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
Not known:	Dyspnoea
These events have been reported after a single dose	
Psychiatric Disorders	
Very rare:	Reversible mental confusion, depression and hallucinations. These adverse reactions have been reported predominantly in severely ill patients, in elderly and in nephropathy 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	
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. 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:Website: www.hpra.ie.

4.9 Overdose

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

Treatment
Symptomatic and supportive therapy should be given as appropriate

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: H_2 – receptor antagonist.
ATC code: A02B A02

Mechanism of action

Ranitidine is a specific, rapidly acting histamine H2-antagonist. It inhibits basal and stimulated secretion of gastric acid, reducing both the volume, and the acid and pepsin content of the secretion.

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

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 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

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 (3-4 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.

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

Potassium Dihydrogen Phosphate
Disodium Hydrogen Phosphate Dihydrate

Sodium Chloride
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

2 years.

6.4 Special precautions for storage

Do not store above 25ºC. Keep ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

2 ml solution in amber, type 1 glass ampoules.
Pack size: 5 ampoules.

6.6 Special precautions for disposal and other handling

Ranitidine Injection has been shown to be compatible with the following intravenous infusion fluids:
Sodium Chloride 0.9% w/v
Dextrose 5% w/v
Sodium Chloride 0.18% w/v and Dextrose 4% w/v
Sodium Bicarbonate 4.2% w/v
Hartmann's solution

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 and would normally not be longer than 24 hours at 2 to 8°C, unless preparation of solutions has taken place in controlled and validated aseptic conditions.
All solutions of Ranitidine Solution for Injection should be discarded after use.

7 MARKETING AUTHORISATION HOLDER

Alliance Pharma (Ireland) Limited
United Drug Distributors, United Drug House
Magna Business Park, Magna Drive
Citywest
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2325/013/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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