SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zantac 150 mg Effervescent Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 150 mg ranitidine (as hydrochloride)

Excipients-contains Aspartame (E951) 30.0 mg, Sorbitol (E420) 1.14 mg and Sodium 327 mg

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Effervescent tablet.

A white to pale yellow, round bevelled tablet marked "GS LHK" on one side and flat on the other which effervesces on dissolution in water to give a clear orange/grapefruit flavoured solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In the treatment of duodenal ulcer and benign gastric ulcer including that associated with non-steroidal anti-inflammatory agents. Prevention of non-steroidal anti-inflammatory drug (including aspirin) associated duodenal ulcers, especially in patients with a history of peptic ulcer disease. Zantac Tablets are also indicated for treatment of post-operative ulcer, reflux oesophagitis, Zollinger-Ellison syndrome and other conditions where reduction of gastric acid secretion is likely to be beneficial.

Children (3 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)

The usual initial dosage is 150 mg bd or 300 mg nocte. This may be increased to ranitidine 300 mg twice daily without an increased incidence of unwanted effects. Subsequently a maintenance dose of 150 mg nocte may be used. Smoking is associated with a higher rate of ulcer relapse, and such patients should be advised to stop smoking. In those who fail to comply with such advice, a dose of 300 mg at night provides additional therapeutic benefit over the standard dose.

In most cases of duodenal ulcer, benign gastric ulcer and post operative ulcer, healing occurs within 4 weeks. Healing usually occurs after a further 4 weeks in those not fully healed after the initial 4 weeks. In ulcers following non-steroidal anti-inflammatory drug therapy, 8 - 12

weeks treatment may be necessary. For the prevention of non-steroidal anti-inflammatory drug associated duodenal ulcers ranitidine 150 mg bd may be given concomitantly with non-steroidal anti-inflammatory drug therapy.

In the management of reflux oesophagitis the usual course of treatment is either 150 mg twice daily or 300 mg at night administered for up to a period of 8, or if necessary 12 weeks. In patients with moderate to severe oesophagitis the dosage may be increased to 150 mg four times daily, alternatively 300 mg twice a day, if necessary.

For the long-term management of reflux oesophagitis, the recommended adult oral dose is 150 mg twice daily for the prevention of relapse in patients with reflux oesophagitis. Zantac 150 mg effervescent tablets are not indicated in patients with complications of reflux oesophagitis e.g. severe oesophegeal stricture or Barratt's oesophagus.

In keeping with the recommended clinical practice it is advisable that patients on long-term maintenance therapy receive regular routine assessment by practitioners.

In patients with Zollinger-Ellison syndrome the starting dose is 150 mg thrice daily, increased as necessary up to a maximum of 6 grams daily.

In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients or the prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration, treatment with Zantac 150 mg twice daily may be substituted for Zantac Injection once oral feeding commences in patients considered to be still at risk from these conditions.

In obstetric patients an oral dose of 150 mg may be given at commencement of labour, followed by 150 mg at 6 hourly intervals. It is recommended that in addition, a non-particulate antacid (e.g. sodium citrate) should be given prior to induction of anaesthesia in any patient requiring emergency general anaesthesia.

Children from 3 to 11 years and over 30 kg of weight

See section 5.2 Pharmacokinetic properties – Special Patient Populations.

Peptic Ulcer Acute Treatment

The recommended oral dose for the treatment of peptic ulcer in children is 4 mg/kg/day to 8 mg/kg/day administered as two divided doses to a maximum of 300 mg ranitidine per day for a duration of 4 weeks. For those patients with incomplete healing, another 4 weeks of therapy is indicated, as healing usually occurs after eight weeks of treatment.

Gastro-Oesophageal Reflux

The recommended oral dose for the treatment of gastro-oesophageal reflux in children is 5 mg/kg/day to 10 mg/kg/day administered as two divided doses to a maximum dose of 600 mg (the maximum dose is likely to apply to heavier children or adolescents with severe symptoms).

Safety and efficacy in new-born patients has not been established

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 that the daily dose of ranitidine in such patients should be 150 mg.

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

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 above in Section 4.2.
Regular supervision of patients who are taking non-steroidal anti-inflammatory drugs concomitantly with 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. 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 medicinal product contains 327 mg sodium per dose, equivalent to 16% of the WHO recommended maximum daily intake for sodium.

The maximum daily dose of this product is equivalent to 65% of the WHO recommended maximum daily intake for sodium.

Zantac Effervescent Tablets is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

As Zantac Effervescent Tablets contain aspartame they should be used with caution in patients with phenylketonuria.

Zantac Effervescent Tablets contain Sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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 keeping with the recommended clinical practice it is advisable that patients on long-term maintenance therapy receive regular routine assessment by practitioners.

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).

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 (see section 5.3).

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, inelderly 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 and tachycardia.

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
Signs and Symptoms
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.

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. Zantac has a relatively long duration of action and so a single 150 mg dose effectively suppresses gastric acid secretion for twelve hours. Clinical evidence has shown that ranitidine combined with amoxycillin and metronidazole eradicates Helicobacter pylori in approximately 90% of patients. This combination therapy has been shown to significantly reduce duodenal ulcer recurrence. Helicobacter pylori infects about 95% of patients with duodenal ulcer and 80% of patients with gastric ulcer.

Although no clear casual link has been established, a large epidemiological study showed an increased risk of developing community acquired pneumonia in current users of H2 receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk increase of 1.63 (95% CI, 1.07 – 2.48). Therefore, in patients with conditions predisposing to the development of pneumonia, such as chronic lung disease, diabetes, or the immunocompromised, there may be an increased risk of developing community acquired pneumonia.

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 include 6% of the dose in urine as 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 ^{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 renal tubular secretion.

Special Patient Populations

Children (3 years and above)

Limited pharmacokinetic data have shown that there are 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 oral ranitidine when correction is made for body weight.

5.3 Preclinical Safety Data

Extensive studies have been carried out in animals. The pharmacology of ranitidine hydrochloride shows it to be a surmountable H_2 receptor antagonist which produces an inhibition of gastric acid secretion. Extensive toxicological investigations have been conducted which predicted a very safe profile for clinical use. This safety has since been confirmed by extensive use in patients for many years.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monosodium citrate anhydrous
Sodium hydrogen carbonate
Aspartame (E951)
Povidone K30
Sodium benzoate (E211)
Orange flavour IFF No.6 (contains Sorbitol (E420))
Grapefruit flavour IFF 18 C222 (contains Sorbitol (E420))

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.
Keep container tightly closed in order to protect from light and moisture.

6.5 Nature and contents of containers

Zantac Effervescent Tablets 150 mg are packed in white polypropylene tubes fitted with white polyethylene caps filled with silica gel. Two tubes are packed into a cardboard carton which has a tamper evident closure. Each tube contains 15 tablets. Alternatively one tube of 10 tablets is packed into a cardboard carton which has a tamper evident closure.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

One or two Zantac Effervescent Tablets should be dissolved in half a tumbler of water (at least 75ml) and stirred thoroughly until completely dissolved before swallowing.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

PA 1077/13/5

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

27th June 1990 / 27th June 2010

10. DATE OF REVISION OF THE TEXT

31st August 2018