Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zantac 150 mg/10 ml Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml of Syrup contains ranitidine hydrochloride equivalent to 150 mg of ranitidine.

Excipients: Each 10 ml of Ranitidine syrup contains:
Approximately 7.5% (800 mg) Ethanol equivalent to 750 mg of pure ethanol
1.5 mg Propyl parahydroxybenzoate (E216)
0.75 mg Butyl parahydroxybenzoate
1 g of Sorbitol

For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Syrup.
A clear, colourless to pale yellow liquid with an odour of mint.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Zantac syrup is used 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 syrup is 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.

See section 4.4 Special warnings and precautions for use.

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 nocte provides additional therapeutic benefit in these patients over the standard dose.

The standard dosage regimen for duodenal or benign gastric ulcer is 150 mg twice daily or 300 mg once nightly. 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 nocte administered for up to a period of eight weeks or if necessary 12 weeks. In patients with moderate to severe oesophagitis the dosage may be increased to 150 mg four times daily; 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 syrup are not indicated in patients with complications of reflux oesophagitis e.g. severe oesophegeal stricture or Barratt's oesophagus.

In patients with Zollinger-Ellison syndrome the starting dose is 150 mg three times 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.

Prophylaxis of Mendelson's Syndrome
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.

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

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 is such patients should be 150 mg.

Children(3 to 11 years)

See section 5.2 Pharmacokinetic properties – Special Patient Populations.

Zantac syrup contains approximately 7.5%w/v ethanol. Therefore an alternative formulation of ranitidine may be considered necessary for at-risk groups; including children (see section 4.4 Special warnings and precautions for use).

PepticUlcer 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 in 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.

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.

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).

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.

Zantac syrup contains approximately 7.5%w/v ethanol (alcohol), i.e. up to 405 mg per 5 ml spoonful which is equivalent to about 11 ml of beer or 5 ml of wine. It is harmful for those suffering from alcoholism. It should be taken into account in pregnant or lactating women, high risk groups (those suffering from alcoholism, liver disease, epilepsy, brain injury or disease) and children (see section 4.2). It may modify or increase the effect of other medicines.

Zantac Syrup contains Sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Patients on prolonged treatment (particularly more than one year) should be kept under regular surveillance.

Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks. Ranitidine should therefore be avoided in patients with a history of acute porphyria.

Patients with hereditary fructose intolerance (HFI), should not take/be given this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per 10 ml, that is to say essentially 'sodium-free'.

This medicine contains potassium, less than 1 mmol (39 mg) per 10 ml, i.e. essentially 'potassium-free'.

This medicine also contains propyl hydroxybenzoate and butyl hydroxybenzoate which may cause allergic reactions (possibly delayed).

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, delaviridine, gefitnib).

Concomitant administration of 300 mg 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 150 mg b.i.d., erlotinib exposure [AUC] and maximum concentrations [Cmax] 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 nephropathic 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 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 Systemand 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 adversereactions
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.

Ranitidine syrup contains approximately 7.5%w/v ethanol (alcohol) (see section 4.4).

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.

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 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 tubular secretion.

Special Patient Populations

Children(3 years andabove)

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.

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.

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. The safety has since been confirmed by extensive use in patients for many years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol
Sodium Chloride
Potassium Dihydrogen Othophosphate
Disodium Hydrogen Orthophosphate Anhydrous
Hypromellose
Propyl parahydroxybenzoate Butyl parahydroxybenzoate Saccharin sodium

Sorbitol 70% non-crystallising
Mint flavour
Purified Water

6.2 Incompatibilities

Dilution of Zantac syrup with syrup BP or sorbitol solution is not recommended as this may result in precipitation.
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened: 2 years.
Once opened: 28 days

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Amber Type III glass bottle fitted with propylene screw cap and a polyester liner or a polypropylene child resistant cap and a LDPE liner containing 300 ml of syrup. A double ended 5 ml/2.5 ml polypropylene spoon is included.

6.6 Special precautions for disposal and other handling

Dilution of Zantac Syrup with syrup BP or sorbitol solution is not recommended as this may result in precipitation.

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA1077/013/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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