Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zantac 150mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150mg ranitidine (as hydrochloride).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Product imported from the UK:
White, round, tablets, engraved ‘GX EC2’ on one side and plain on the other.

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

Adults (including the elderly) / Adolescents (12 years and over)
The usual initial dosage in duodenal and benign gastric ulcer is 150mg twice daily or 300mg at night. This may be increased to ranitidine 300mg twice daily without an increased incidence of unwanted effects. Subsequently a maintenance dose of 150mg at night 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 300mg 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 with 150mg twice daily or 300mg at night. For the prevention of non-steroidal anti-inflammatory drug associated duodenal ulcers, ranitidine 150mg twice daily may be given concomitantly with non-steroidal anti-inflammatory drug therapy.

In the management of reflux oesophagitis the usual course of treatment is either 150mg twice daily or 300mg 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 150mg four times daily, alternatively 300mg twice a day, if necessary.

For the long-term management of reflux oesophagitis, the recommended adult oral dose is 150mg twice daily for the prevention of relapse in patients with reflux oesophagitis. Zantac Tablets 150mg 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 their practitioners.

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

In obstetric patients an oral dose of 150mg may be given at commencement of labour, followed by 150mg 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 4mg/kg/day to 8mg/kg/day administered as two divided doses to a maximum of 300mg 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 5mg/kg/day to 10mg/kg/day administered as two divided doses in a maximum dose of 600mg (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.

Renal Insufficiency:-
Accumulation of ranitidine with resulting elevated plasma concentrations will occur in patients with renal impairment (creatinine clearance less than 50ml/min). It is recommended that the daily dose of ranitidine in such patients should be 150mg.

4.3 Contraindications

Use in patients known to have hypersensitivity to any component of the preparation.

4.4 Special warnings and precautions for use

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

Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks. Ranitidine should, therefore, be avoided in patients with a history of acute porphyria.
Before initiation of ranitidine treatment for any gastric ulceration, malignancy should be excluded by endoscopy and biopsy if possible. Treatment may mask the symptoms of malignancy, delaying diagnosis.

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 section 4.2 Posology and method of administration.

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.

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) or a decrease in absorption (e.g. ketoconazole, atazanavir, glipizide, delaviridine, gefitnib).

4.6 Fertility, pregnancy and lactation

Ranitidine should not be administered during pregnancy or lactation unless considered essential by the physician. Ranitidine crosses the placenta and has been detected in breast milk.

4.7 Effects on ability to drive and use machines

Not applicable.

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

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_2 receptor antagonists bradycardia and A-V Block.

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)

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

Ranitidine is very specific in action and no particular problems are expected following overdosage with the drug. 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 150mg dose effectively suppresses gastric acid secretion for twelve hours.

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 150mg ranitidine, maximum plasma concentrations (300 to 550ng/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 300mg.

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 150mg ^{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 150mg ^{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 500mL/min, which exceeds glomerular filtration indicating net 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

Microcrystalline cellulose
Magnesium stearate
Hypromellose
Titanium dioxide (E171)
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister strips in an overlabelled outer carton, containing 60 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1328/105/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th June 2009

10 DATE OF REVISION OF THE TEXT

November 2012