Zantac Syrup

1. NAME OF THE MEDICINAL PRODUCT

Zantac Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml of syrup contains Ranitidine Hydrochloride 168.0 mg (Equivalent to Ranitidine 150.0 mg)

Each 10 ml of syrup also contains the following excipients:
- 800 mg ethanol
- 1.5 mg propyl Parahydroxybenzoate
- 0.75 mg butyl Parahydroxybenzoate
- 1000 mg Sorbitil Liquid (Non-crystallising)

For the full list of excipients, see section 6.1

The preparation contains: Ethanol (96%)
The amount of ethanol per bottle (300 ml): 24 grams
The amount of ethanol in every 10 ml:800 mg
The concentration of ethanol in the preparation: approximately 7.5% w/v

3. PHARMACEUTICAL FORM

Syrup

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:

Zantac syrup is indicated for the treatment of duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents. Zantac syrup is also indicated for the treatment of post-operative ulcer, Zollinger-Ellison Syndrome and oesophageal reflux disease including long term management of healed oesophagitis. Zantac syrup is indicated for the following conditions where reduction of gastric secretion and acid output is desirable; the prophylaxis of gastro-intestinal haemorrhage from stress ulceration in seriously ill patients and before general anaesthesia in patients considered to be at risk of acid aspiration (Mendelson's Syndrome), particularly obstetric patients during labour. For appropriate cases Zantac injection is also available (see separate Physician Leaflet).

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)
The usual dosage is 150 mg twice daily, taken in the morning and evening. Alternatively, patients with duodenal ulceration, gastric ulceration or oesophageal reflux disease may be treated with a single bedtime dose of 300 mg. It is not necessary to time the dose in relation to meals.

Duodenal ulcer, benign gastric ulcer and post-operative ulcer:
In most cases of duodenal ulcer, benign gastric ulcer and post operative ulcer, healing occurs in four weeks. Healing usually occurs after a further 4 weeks of treatment in those patients whose ulcers have not fully healed after the initial course of therapy.

NSAID associated peptic ulceration:
In ulcers following non-steroidal anti-inflammatory drug therapy or associated with continued non-steroidal anti-inflammatory drugs, 8 weeks treatment may be necessary.

In duodenal ulcer 300 mg twice daily for 4 weeks results in healing rates which are higher than those at 4 weeks with ranitidine 150 mg twice daily or 300 mg nocte. The increased dose has not been associated with an increased incidence of unwanted effects.

Maintenance treatment at a reduced dosage of 150 mg at bedtime is recommended for patients who have responded to short term therapy, particularly those with a history of recurrent ulcer.

Gastro-oesophageal reflux disease:
In the management of oesophageal reflux disease, the recommended course of treatment is either 150 mg twice daily or 300 mg at bedtime for up to 8 weeks or if necessary 12 weeks.

In patients with moderate to severe oesophagitis, the dosage of ranitidine may be increased to 150 mg four times daily for up to twelve weeks. The increased dose has not been associated with an incidence of unwanted effects.

For the long-term management of oesophagitis the recommended adult oral dose is 150 mg twice daily. Long-term treatment is not indicated in the management of patients with unhealed oesophagitis with or without Barrett's epithelium.

Zollinger-Ellison syndrome:
In patients with Zollinger-Ellison Syndrome, the starting dose is 150 mg three times daily and this may be increased as necessary. Patients with this syndrome have been given increasing doses up to 6 g per day and these doses have been well tolerated.

Prophylaxis of haemorrhage from stress ulceration:
In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients, treatment with Zantac tablets 150 mgs twice daily may be substituted for Zantac injection once oral feeding commences in patients considered to be still at risk from this condition.

Prophylaxis of Mendelson's syndrome:
In patients thought to be at risk of acid aspiration syndrome an oral dose of 150 mg can be given 2 hours before induction of general anaesthesia, and preferably also 150 mg the previous evening.

In obstetric patients at commencement of labour, an oral dose of 150 mg may be given followed by 150 mg at six hourly intervals. It is recommended that since gastric emptying and drug absorption are delayed during labour, any patient requiring emergency general anaesthesia should be given, in addition, a non-particulate antacid (eg sodium citrate) prior to induction of anaesthesia. The usual precautions to avoid acid aspiration should also be taken.

Children 12 years and over
For children 12 years and over the adult dosage is given.

Children (3 to 11 years)
See Section 5.2 Pharmacokinetic properties (Other special 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).

Patients over 50 years of age
See Section 5.2 Pharmacokinetic properties (Other special 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 of 600 mg (the maximum dose is likely to apply to heavier children or adolescents with severe symptoms).

Neonates
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). Accordingly, it is recommended that the daily dose of ranitidine in such patients be 150 mg at night for 4 to 8 weeks. The same dose should be used for maintenance treatment if necessary. If an ulcer has not healed after treatment, the standard dosage regimen of 150 mg twice daily should be instituted, followed, if need be, by maintenance treatment at 150 mg at night.

Method of administration
For oral administration.

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

Malignancy
The possibility of malignancy should be excluded before commencement of therapy in patients with gastric ulcer and in patients of middle age and over with new or recently changed dyspeptic symptoms 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.

Regular supervision of patients who are taking non-steroidal anti-inflammatory drugs concomitantly with ranitidine is recommended, especially in the elderly. Current evidence shows that ranitidine protects against NSAID associated ulceration in the duodenum and not in the stomach.

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

Rates of healing of ulcers in clinical trial patients aged 65 and over have not been found to differ from those in younger patients. Additionally, there was no difference in the incidence of adverse effects.

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 effects of other medicines.

Zantac Syrup contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Alternative formulation of Zantac may be considered preferential in these populations.

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).

4.5 Interaction with other medicaments 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, propanolol 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 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).

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 or 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

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 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 Effect 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

Not known: 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 patients, 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 and tachycardia.

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 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il// Additionally, you should also report to GSK Israel (il.safety@gsk.com).

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: H2-receptor antagonists
ATC code: A02BA02

Mechanism of action

Ranitidine is a specific, rapidly acting H_2-antagonist. It inhibits basal and stimulated secretion of gastric acid, reducing both the volume of the acid and pepsin content of the secretion. Ranitidine has a relatively long duration of action and a single 150 mg dose effectively suppresses gastric acid secretion for twelve hours.

5.2 Pharmacokinetic properties

Following oral administration of 150 mg ranitidine, maximum plasma concentrations (300 to 550 ng/mL) occurred after 1—3 hours. Two distinct peaks or 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 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.

Other special populations

Children (3 years and above)

Limited pharmacokinetic data show 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.

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.

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

Sorbitol solution
Ethanol (96%)
Mint flavour IFF 17: 42: 3632
Hydroxypropyl methylcellulose
Disodium hydrogen orthophosphate anhydrous
Sodium chloride
Potassium dihydrogen orthophosphate

Saccharin sodium
Propyl Parahydroxybenzoate
Butyl Parahydroxybenzoate
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the label and packaging.

After the first opening use within 28 days.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Amber glass bottle with screw cap or polypropylene child resistant cap.
Pack size: 300 ml.

6.6 Special precautions for disposal and other handling

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer

Aspen Bad Oldesloe GmbH, Bad Oldesloe, Germany

8. License Holder and Importer

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva

9. License Number

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