ZANTAC
Tablets/Dispersible Tablets/Syrup

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

ZANTAC Tablets

ZANTAC 300 mg Tablets

ZANTAC Effervescent 150 Tablets

ZANTAC Effervescent 300 Tablets

ZANTAC Syrup

COMPOSITION:

ZANTAC Tablets: Each tablet contains ranitidine 150 mg (as the hydrochloride).

ZANTAC 300 mg Tablets: Each tablet contains ranitidine 300 mg (as the hydrochloride).

The excipients include:

Tablet core: Croscarmellose sodium (300 mg tablet only), magnesium stearate and microcrystalline cellulose.

Film coat: Hydroxypropyl cellulose, hydroxypropyl methylcellulose 2910 and titanium dioxide (E171).

Sugar-free.

ZANTAC Effervescent 150 Tablets: Each effervescent tablet contains ranitidine 150 mg (as the hydrochloride).

Contains sugar (sorbitol): 1,14 mg/tablet.

These tablets contain aspartame as a sweetening agent and sodium benzoate.

ZANTAC Effervescent 300 Tablets: Each effervescent tablet contains ranitidine 300 mg (as the hydrochloride).

Contains sugar (sorbitol): 1,71 mg/tablet.

These tablets contain aspartame as a sweetening agent and sodium benzoate.

The other excipients include grapefruit flavour IFF 18 C222, monosodium citrate anhydrous, orange flavour IFF 6, povidone K30 and sodium bicarbonate.

ZANTAC Syrup: Each 10 ml dosage contains 150 mg ranitidine (as the hydrochloride). ZANTAC Syrup contains propylhydroxybenzoate 0,015 % *m/v*, butylhydroxybenzoate 0,0075 % *m/v* and ethanol 7,5 % *m/v* as preservatives.

Contains sugar (as sorbitol solution 5 g/10 ml) and saccharin sodium as a sweetening agent.

The other excipients are: disodium hydrogen orthophosphate anhydrous, hydroxypropyl methylcellulose, mint flavour, potassium dihydrogen orthophosphate, purified water and sodium chloride.

PHARMACOLOGICAL CLASSIFICATION:

A 11.4.3 Medicines acting on gastro-intestinal tract. Antacids - other

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

ZANTAC is a selective and competitive histamine H_2-receptor antagonist and does not exhibit anti-serotonergic or histamine H_1-receptor blocking activities, nor does it show any measurable affinity for androgen, oestrogen, progesterone, glucocorticoid or mineralocorticoid receptors, nor does it affect serum prolactin concentrations.

It inhibits basal and stimulated secretion of gastric acid, reducing both the volume of secretions and the acid and pepsin content but does not affect gastric mucous secretion.

Pharmacokinetic properties:

Absorption: Following oral administration of 150 mg ranitidine, maximum plasma concentrations occurred after 1-3 hours. Two distinct peaks or a plateau in the absorption phase result from the re-absorption of ranitidine excreted into the intestine. The absolute bioavailability of ranitidine is 50-60 % and plasma concentrations increase proportionately with increasing doses up to 300 mg.

Absorption is not impaired by foods or antacids.

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 IV dosing and includes 6 % of the dose in urine as the N-oxide, 2 % as the S-oxide, 2 % as desmethyl ranitidine and 1-2 %

as the furoic acid analogue. Ranitidine generally does not interact with the cytochrome P450-linked drug metabolising enzyme system.

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 ranitidine. 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 substance. Less than 3 % of ranitidine is excreted in bile. Renal clearance is approximately 500 ml/min, which exceeds glomerular filtration indicating net renal tubular secretion.

Special Patient Populations:

Patients over 50 years of age: In patients over 50 years of age, half-life is prolonged (3-4 hours) 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.

INDICATIONS:

ZANTAC is indicated for the treatment of duodenal ulcers; benign gastric ulcer; including prevention of duodenal ulceration associated with non-steroidal anti-inflammatory agents, reflux oesophagitis and Zollinger-Ellison Syndrome.

For duodenal ulcers associated with *Helicobacter pylori* infection, ZANTAC may be used in combination with appropriate antibiotics.

ZANTAC may also be used as premedication prior to anaesthesia in order to reduce the volume and acid content of gastric secretion, thereby minimising the consequence of the acid aspiration syndrome.

CONTRA-INDICATIONS:

ZANTAC is contra-indicated in patients known to have hypersensitivity to any component of the preparation.

WARNINGS AND SPECIAL PRECAUTIONS:

The possibility of malignancy should be excluded before commencement of therapy in patients with gastric ulcer, as treatment with ZANTAC may mask symptoms of gastric carcinoma.

ZANTAC should be avoided in patients with a history of acute porphyria.

Ranitidine is excreted via the kidneys and so plasma levels are increased and prolonged in patients with renal impairment (below a Cl_{Cr} of 50 ml/min). Accordingly, it is recommended that the dose be reduced to 150 mg daily.

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 H_2 receptor antagonists, such as ZANTAC, versus those who had stopped treatment, with an observed adjusted relative risk increase of 1,63 (95 % CI, 1,07-2,48).

Care should be taken to carry out periodic examinations of patients on prolonged maintenance treatment with ZANTAC as a safeguard against the occurrence of unforeseeable consequences of treatment.

Regular supervision of patients who are taking non-steroidal anti-inflammatory agents concomitantly with ZANTAC is recommended, especially if elderly.

Current evidence shows that ranitidine protects against NSAID-associated ulceration in the duodenum and not in the stomach.

ZANTAC Effervescent Tablets:

As ZANTAC Effervescent 150 and 300 Tablets contain aspartame they should be used with caution in patients with phenylketonuria.

ZANTAC Effervescent 150 and 300 Tablets contain sodium (14,2 mmol/327 mg and 20,7 mmol/476 mg, respectively).

Care should therefore be taken in treating patients in whom sodium restriction is indicated.

ZANTAC Syrup:

ZANTAC syrup contains approximately 7,5 % *m/v* ethanol (alcohol), i.e. up to 405 mg per 5 ml spoonful. 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 DOSAGE AND DIRECTIONS FOR USE). It may modify or increase the effect of other medicines.

ZANTAC syrup contains propyl- and butylhydroxybenzoate which may cause allergic reactions (possibly delayed).

Patients with the rare hereditary condition of sorbitol intolerance should not take ZANTAC Syrup.

INTERACTIONS:

Ranitidine has the potential to affect the absorption, metabolism or renal excretion of other medicines. The altered pharmacokinetics may necessitate dosage adjustment of the affected medicine or discontinuation of treatment.

Interactions occur by several mechanisms including:

1) **Inhibition of cytochrome P450-linked mixed function oxygenase system:**

ZANTAC at usual therapeutic doses does not potentiate the actions of medicines which are inactivated by this enzyme system such as diazepam, lidocaine (lignocaine), phenytoin, propranolol and theophylline.

There have been reports of altered prothrombin time/INR with anticoagulants (e.g. warfarin). Due to the narrow therapeutic index, close monitoring of increased or decreased prothrombin time is recommended during concurrent treatment with ZANTAC.

2) **Competition for renal tubular secretion:**

Since ranitidine is partially eliminated by the cationic system, it may affect the clearance of other medicines eliminated by this route. High doses of ZANTAC (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 medicines.

3) **Alteration of gastric pH:**

The bioavailability of certain medicines 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, itraconazole, atazanavir, delaviridine, gefitinib).

There is no evidence of an interaction between ZANTAC, amoxicillin or metronidazole.

If high doses (2 g) of sucralfate are co-administered with ZANTAC the absorption of the latter may be reduced. This effect is not seen if sucralfate is taken after an interval of 2 hours.

PREGNANCY AND LACTATION:

Pregnancy: Safety in pregnancy has not been established.

Lactation: Safety in lactating women has not been established.

DOSAGE AND DIRECTIONS FOR USE:

ZANTAC Effervescent 150 or 300 tablets should be placed in half a glass of water (minimum 75 ml or 150 ml, respectively) and allowed to dissolve completely before swallowing.

ADULTS:

In Peptic Ulceration: The usual dosage is 150 mg twice daily, taken in the morning and before retiring, or a single bedtime dose of 300 mg. It is not necessary to time the dose in relation to meals. In most cases of duodenal ulcer and benign gastric ulcer, healing may occur in four weeks. Ulcers that do not heal within 4 weeks may require a further course of treatment. In ulcers following non-steroidal anti-inflammatory therapy or

associated with continued non-steroidal anti-inflammatory agents, 8-12 weeks treatment may be necessary.

For the prevention of non-steroidal anti-inflammatory agent associated duodenal ulcers, ZANTAC 150 mg twice daily may be given concomitantly with non-steroidal anti-inflammatory agent therapy.

For duodenal ulcers associated with *Helicobacter pylori* infection, ZANTAC may be used in combination with appropriate antibiotics.

In Reflux Oesophagitis: To help in the management of reflux oesophagitis, the recommended course of treatment is 150 mg twice daily or 300 mg at bedtime for up to 8, or if necessary, 12 weeks. In patients with moderate to severe reflux oesophagitis, the dosage may be increased to 150 mg four times daily for up to 12 weeks.

For the long-term management of reflux oesophagitis the recommended adult oral dose is 150 mg twice daily.

In Zollinger-Ellison Syndrome: In patients with very high gastric acid secretion (e.g. Zollinger-Ellison Syndrome) the starting dose is 150 mg three times daily and this may be increased as necessary, to within the range of 600 mg to 900 mg per day.

In Anaesthesia: For premedication prior to anaesthesia in order to reduce the volume and acid content of gastric secretion, a dose of 300 mg given at least 2 hours before induction is indicated to minimise the consequences of the acid aspiration syndrome. Alternatively, a dose of 150 mg given 12 hours prior, followed by a further 150 mg 2 hours prior to anaesthesia, is effective in suppressing gastric secretion.

Maintenance Treatment: For patients with peptic ulceration who have responded to short-term therapy, particularly those with a history of recurrent ulcer, extended maintenance treatment at a reduced dosage of 150 mg at bedtime is advised.

Smoking is associated with a higher rate of ulcer relapse. Patients should be advised to stop smoking. In patients unable to stop smoking, a dose of 300 mg at night provides additional therapeutic benefit in these patients over the 150 mg dosage regimen.

Children:

Experience with ZANTAC in children is limited and such use has not been fully evaluated in clinical studies.

Renal impairment:

Ranitidine is excreted via the kidneys and so plasma levels of the medicine are increased and prolonged in patients with renal impairment (below a Cl_{Cr} of 50 ml/min). Accordingly, it is recommended that the dose be reduced to 150 mg daily.

Pharmaceutical Precautions: Dilution of ZANTAC Syrup with Syrup BP or Sorbitol solution is not recommended as this may result in precipitation. ZANTAC Syrup should not be diluted or admixed with other liquid preparations.

SIDE EFFECTS:

Blood and Lymphatic System Disorders:

Less frequent: blood count changes (leucopenia, thrombocytopenia), agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or marrow aplasia

Immune System Disorders:

Less frequent: hypersensitivity reactions (urticaria, angioedema, fever, bronchospasm, hypotension and chest pain), anaphylactic shock

These reactions have been reported after a single dose.

Psychiatric Disorders:

Less frequent: reversible mental confusion, depression and hallucinations

Nervous System Disorders:

Less frequent: headache (sometimes severe), dizziness and involuntary movement disorders

Cardiac Disorders:

Less frequent: bradycardia and AV block

Vascular Disorders:

Less frequent: vasculitis

Gastrointestinal Disorders:

Less frequent: acute pancreatitis, constipation, diarrhoea, nausea and vomiting

Hepatobiliary Disorders:

Less frequent: transient and reversible changes in liver function tests, hepatitis (hepatocellular, hepatocanalicular or mixed) with or without jaundice

Skin and Subcutaneous Tissue Disorders:

Less frequent: skin rash**,** erythema multiforme, alopecia

Musculoskeletal and Connective Tissue Disorders:

Less frequent: musculoskeletal symptoms such as arthralgia and myalgia

Renal and Urinary Disorders:

Less frequent: acute interstitial nephritis

Reproductive and Breast Disorders:

Less frequent: reversible impotence, breast symptoms (discomfort, pain and/or swelling), and breast conditions (such as gynaecomastia and galactorrhoea).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See Side effects. Symptomatic and supportive therapy should be given as appropriate.

IDENTIFICATION:

ZANTAC Tablets: A white, film-coated round biconvex tablet engraved on one face with 'GXEC2' and plain on the other.

ZANTAC 300 mg: White, film-coated, capsule-shaped tablets, engraved on one side with 'GXEC3' and plain on the other.

ZANTAC Effervescent 150: White to pale yellow, round, bevelled tablets marked 'GS LHK' on one side and flat on the other, which effervesces on dissolution to give a clear, colourless, grapefruit/orange flavoured solution.

ZANTAC Effervescent 300: White to pale yellow, round, bevelled tablets marked 'GS MJG' on one side and flat on the other, which effervesces on dissolution to give a clear, colourless, grapefruit/orange flavoured solution.

ZANTAC Syrup: A clear, pale yellow liquid with the odour of mint.

PRESENTATION:

ZANTAC Tablets: Cartons of 30 and 60 tablets foil wrapped.

ZANTAC 300 mg: Cartons of 30 tablets foil wrapped.

ZANTAC Effervescent 150: Carton containing 1 or 2 tubes of 14 or 15 effervescent tablets.

ZANTAC Effervescent 300: Carton containing 1 or 2 tubes of 14 or 15 effervescent tablets each.

ZANTAC Syrup**:** 300 ml amber glass bottles, fitted with a polypropylene cap.

STORAGE INSTRUCTIONS:

ZANTAC Tablets, 300 mg Tablets, Effervescent 150 or 300 Tablets:

Store in a dry place at or below 30 °C.

Store in the original package to protect from moisture

ZANTAC Syrup: Store at or below 25 °C.

Keep out of reach of children.

REGISTRATION NUMBER:

ZANTAC Tablets: P/11.4.3/218

ZANTAC 300 mg: S/11.4.3/378

ZANTAC Effervescent 150: Z/11.4.3/303

ZANTAC Effervescent 300: Z/11.4.3/304

ZANTAC Syrup: W/11.4.3/277

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

Registration date:

ZANTAC Tablets: 07 September 1982

ZANTAC 300 mg: 11 August 1986

ZANTAC Effervescent 150: 01 September 1992

ZANTAC Effervescent 300: 26 June 1992

ZANTAC Syrup: 11 March 1991

Revision approval date: 30 September 2016

GDS-45

HISTORY:

Amended: 15 May 2002 (Company name change – merger) (Deletion of 14 pack size for Zantac 300)
Amended: 04 April 2003 (Change in tablet description) – Approved 01/01/2005
Amended: 24 March 2003 (Responding to MCC recommendations – In process with CCC
30-04-2008: Correction to tablet description (D2008 – 0814)
Amended: 02 September 2010 (Resubmission of Response 24/03/2003 + New safety data)
Amended: 14 April 2011 change in ID, presentation and applicant address annotated
Amended: 19 July 2011 (in response to CCC recommendations dated 20/06/2011) – approved 2012.03.02
Amended: 31 July 2012 (in line with GDS versions 42-43) – annotated
Amended: 24 June 2014 (in response to CCC recommendations dated 10/03/2014, received 15/04/14)D2014-3162
Amended: 07 April 2016 (in response to CCCR dated 03/12/2015)
Amended: 12 July 2016 (in response to CCCR dated 04/07/2016), approved 30.09.2016
Amended: 14 May 2018: Update to the storage conditions in line with GDS45, amendment to composition and presentation in line with registered detail - Implemented 15 May 2018