

PRODUCT SUMMARY

1. NAME OF THE MEDICINAL PRODUCT

Ranitidine 300mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Ranitidine hydrochloride Ph.Eur. equivalent to Ranitidine 300 mg

3. PHARMACEUTICAL FORM

Oblong, biconvex, white to yellowish film-coated biconvex tablet. Tablet size: 8.2 x 17mm.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Adults:

Goldshield Ranitidine tablets are indicated in the treatment of ulcers of the duodenum and of benign gastric ulcers, including those associated with use of non-steroidal anti-inflammatory agents (NSAID's) and/or prevention of NSAID induced duodenal ulcers.

Goldshield Ranitidine tablets may also be used in conditions where reduction of gastric secretion and acid output may be beneficial, such as: prophylaxis of gastrointestinal haemorrhage arising from stress ulceration in seriously ill patients; prophylaxis of recurring haemorrhage associated with bleeding peptic ulcers; before general anaesthesia in patients considered to be at risk of acid aspiration (Mendelson's syndrome) for example in obstetric patients during labour.

Other indications include the treatment of Zollinger-Ellison syndrome, gastro-oesophageal reflux disease (including the long-term management of healed oesophagitis) and post-operative ulcer. Patients with chronic episodic dyspepsia, characterised by pain (epigastric or retrosternal) which disturbs sleep or is related

to meals but is not associated with the preceding conditions may also benefit from treatment with Goldshield Ranitidine.

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 and the elderly:

Treatment of ulcers

The normal starting dose is Goldshield Ranitidine 150 mg twice daily, morning and evening. Absorption is not affected by the presence of food.

Patients with duodenal ulceration, gastric ulceration or gastro-oesophageal reflux disease may be treated with a single dose of 300 mg at bedtime. In duodenal ulcer it has been reported that use of 300 mg twice daily for 4 weeks results in healing rates which are higher than those at 4 weeks with ranitidine 150mg twice daily or 300 mg nocte, without an associated increase in the incidence of adverse reactions.

In most cases of duodenal ulcer, benign gastric ulcer and post-operative ulcer, healing occurs in four weeks. A further four week course of treatment may be necessary in those patients whose ulcers have not fully healed after the initial course of therapy; healing normally takes place following the second course of treatment.

NSAID associated ulcers

In ulcers following NSAID therapy or associated with continued NSAID's, eight weeks' treatment may be necessary to induce healing.

For the prevention of NSAID associated duodenal ulcers, Goldshield Ranitidine 150mg twice daily may be given with NSAID therapy.

Maintenance treatment of ulcers

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.

Oesophageal Reflux Disease

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

In patients with moderate to severe gastro-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 increased incidence of adverse reactions.

The recommended adult oral dose is 150 mg twice daily for the long-term treatment of healed oesophagitis. Long-term treatment is not indicated in the management of patients with unhealed oesophagitis.

Mendelson's Syndrome

Goldshield Ranitidine tablets 150 mg can be given orally 2 hours before induction of general anaesthesia, and if possible, an additional dose of 150 mg the previous evening, in patients regarded to be at risk of acid aspiration syndrome.

At onset of labour, an oral dose of 150 mg Goldshield Ranitidine may be given to obstetric patients followed by a further 150 mg every six hours. Since gastric emptying and drug absorption are delayed during labour, it is recommended that any patient requiring emergency general anaesthesia should also be given a non-particulate antacid (e.g. sodium citrate) prior to induction of anaesthesia. The usual precautions to avoid acid aspiration should also be taken.

Zollinger-Ellison syndrome

In patients with Zollinger-Ellison syndrome, the recommended starting dose is 150 mg three times daily, which may be increased as necessary. Doses increasing to 6 g per day have been used in patients with this syndrome and it has been reported that these doses have been well tolerated.

Chronic episodic dyspepsia

The recommended course of treatment in such cases is 150 mg twice daily for up to six weeks. Further investigations should be carried out in non-responding patients.

Children

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 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

Ranitidine products are contraindicated in patients known to have hypersensitivity to any component of the preparation.

4.4 Special warnings and precautions for use

The possibility of malignancy should be excluded before commencement of therapy in patients with gastric ulcer [and if indications include dyspepsia; patients of middle age and over with new or recently changed dyspeptic symptoms must be included] as treatment with ranitidine may mask symptoms of gastric carcinoma.

As Ranitidine is excreted via the kidney, plasma levels of the drug are increased in patients with severe renal impairment. It is therefore recommended that a reduced starting dose of Goldshield Ranitidine is utilised in such patients ie.150 mg at night for 4 to 8 weeks. The same dose should be used for maintenance treatment if deemed necessary. If an ulcer has not healed after treatment the standard dosage regimen of 150 mg twice daily may be commenced, followed, if necessary, by maintenance treatment of 150mg at night.

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 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 H2 receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk increase of 1.82 (95% CI, 1.26 -2.64). **This increased risk was mainly observed in patients with pulmonary diseases, diabetes, heart failure and in immunocompromised patients.**

Current evidence shows that Ranitidine only protects against NSAID associated ulceration in the duodenum, not in the stomach. Regular supervision of all patients, but

especially the elderly, who are taking NSAID's concomitantly with Ranitidine is recommended.

Use in renal transplants

Ranitidine has been used successfully in patients with renal transplants.

Use in elderly patients

Similar rates of healing of ulcers and adverse reaction profiles have been observed in patients aged 65 and over compared to younger patients.

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 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, gefitinib).

Oral Formulations:

There is no evidence of an interaction between ranitidine and metronidazole and amoxicillin. 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 h.

4.6 Pregnancy and lactation

Pregnancy

Ranitidine crosses the placenta but therapeutic doses administered to obstetric patients in labour or undergoing caesarean section at the recommended dosage (see sections 4.1 & 4.2) 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.

Lactation

Ranitidine is excreted in human breast milk. Like other drugs ranitidine should only be used during nursing if considered essential.

4.7 Effects on ability to drive and use machines

Ranitidine may cause dizziness and the patient should be warned not to drive or to operate machinery if affected.

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 postmarketing 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.

Vascular Disorders

Very Rare: Vasculitis.

Gastrointestinal Disorders

Very Rare: Acute pancreatitis.

Uncommon: abdominal pain, diarrhoea, 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 galactorrhea).

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.

4.9 Overdose

Symptoms and Signs

Ranitidine is very specific in action and no particular problems are expected following overdosage with ranitidine formulations.

Treatment

No specific antidote is available. Ranitidine may be removed from the plasma by haemodialysis. Symptomatic and supportive therapy should be given as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Ranitidine is a specific, rapidly acting histamine H₂ -antagonist. It inhibits both basal and stimulated secretion of gastric acid, thereby reducing both the volume and the acid and pepsin content of gastric secretions. Ranitidine has a relatively long duration of action. A single dose effectively suppresses gastric acid secretion for up to twelve hours.

5.2. Pharmacokinetic Properties

Absorption of ranitidine after oral administration is rapid and peak plasma concentrations are usually achieved 2-3 hours after administration. Absorption is not significantly impaired by food or antacids. Oral bioavailability is approximately 50%.

Ranitidine is approximately 15% protein bound.

Metabolism of ranitidine is not extensive, and elimination of the drug is primarily by tubular secretion. The elimination half-life of ranitidine is 2-3 hours. In

balance studies with 150 mg 3H-ranitidine 60-70% of an oral dose was excreted in urine and 26% in faeces. 35% of the oral dose was eliminated unchanged in the urine in the first 24 hours after dosing. Approximately 6% of the dose is excreted as the N-oxide, 2% as the S-oxide, 2% as desmethyl ranitidine and 1-2% as the furoic acid analogue.

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. Pre-clinical Safety Data

There was no indication of tumourigenic or carcinogenic effects in life-span studies in mice and rats at dosages up to 2,000 mg/kg per day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella*, *Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Croscarmellose sodium Ph.Eur

Magnesium stearate Ph.Eur.

Microcrystalline cellulose Ph.Eur.

Hydroxypropylmethylcellulose Ph.Eur.

Titanium dioxide Ph.Eur.

Talc Ph.Eur.

Polyethylene glycol 6000 Ph Eur

Polymethylmethacrylic acid copolymer (Eudragit E)

6.2. Incompatibilities

None known.

6.3. Shelf Life

2 years (unopened).

6.4. Special Precautions for Storage

Store below 25°C in a dry place.

6.5. Nature and Contents of Container

Carton of 30 tablets, packed in A1/A1 blisters.

6.6. Instructions for Use/Handling

No special requirements.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Ltd.
NLA Tower, 12-16 Addiscombe Road
Croydon,
CR0 0XT
United Kingdom.

8. MARKETING AUTHORISATION NUMBER(S)

PL 12762/0012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

27 October 1997

10 DATE OF REVISION OF THE TEXT

19/07/2010