

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ranitidine 300mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains ranitidine 300 mg (as the hydrochloride).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film coated tablets.

White to almost white, oblong, biconvex, film coated tablets embossed with “B” and “L” on either side of the breakline on one side and “300” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Ranitidine Tablets are indicated for:

- Treatment of duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents.
- Treatment of duodenal ulcers associated with *Helicobacter pylori* infection.
- Treatment of post-operative ulcer
- Zollinger-Ellison syndrome
- Oesophageal reflux disease
- Chronic episodic dyspepsia, characterised by pain (epigastric or retrosternal) which is related to meals or disturbs sleep but is not associated with the preceding conditions may benefit from ranitidine treatment.

Ranitidine Tablets are indicated for the following conditions where reduction of gastric secretion and acid output is desirable:

- prophylaxis of gastrointestinal haemorrhage from stress ulceration in seriously ill patients
- prophylaxis of recurrent haemorrhage in patients with bleeding peptic ulcers
- before general anaesthesia in patients considered to be at risk of acid aspiration (Mendelson's syndrome), particularly obstetric patients during labour.

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

Posology

Adults (including the elderly):

The usual dosage is 150 mg twice daily, taken in the morning and evening.

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 four weeks of treatment in those patients whose ulcers have not fully healed after the initial course of therapy.

NSAID associated peptic ulceration, including prophylaxis of duodenal ulcers:

In ulcers following non-steroidal anti-inflammatory drug therapy or associated with continued non-steroidal anti-inflammatory drugs, eight 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 at night. The increased dose has not been associated with an increased incidence of unwanted effects.

Duodenal ulcers associated with Helicobacter pylori infection:

For duodenal ulcers associated with *Helicobacter pylori* infection ranitidine 300 mg at bedtime or 150 mg twice daily may be given with oral amoxicillin 750 mg three times daily and metronidazole 500 mg three times daily for two weeks. Therapy with ranitidine should continue for a further 2 weeks. This dose regimen significantly reduces the frequency of duodenal ulcer recurrence.

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 300 mg at bedtime for up to 8 weeks or if necessary 12 weeks.

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.

Chronic episodic dyspepsia:

For patients with chronic episodic dyspepsia the recommended course of treatment is 150 mg twice daily for up to six weeks. Anyone not responding or relapsing shortly afterwards should be investigated.

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 Ranitidine Tablets 150 mg twice daily may be substituted for Ranitidine Injection once oral feeding commences in patients considered to be still at risk from these conditions.

Prophylaxis of acid aspiration (Mendleson'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 (e.g. 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 from 3 to 11 years and over 30kg of weight:

See Section 5.2 Pharmacokinetic Properties (Special Patient Populations)

Peptic Ulcer Acute Treatment:

The recommended oral dose for 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 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 over 50 years of age:

See Section 5.2 Pharmacokinetic Properties (Special Patient Populations, Patients over 50 years of age)

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 should be 150 mg at night for 4-8 weeks. The same dose should be used for maintenance treatment, if necessary. If an ulcer has not healed after treatment, 150 mg twice daily dosage should be instituted followed, if need be, by maintenance treatment of 150 mg at night.

Method of administration

Oral administration.

The tablets have to be swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Although clinical reports of acute intermittent porphyria associated with ranitidine administration have been rare and inconclusive, ranitidine should be avoided in patients with a history of this condition.

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 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.

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 above under section 4.2 in renal impairment.

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.

Although clinical reports of acute intermittent porphyria associated with ranitidine administration have been rare and inconclusive, ranitidine should be avoided in patients with a history of this condition

Use in elderly patients:

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 medicinal products and other forms of interaction

Regular supervision of patients who are taking NSAIDs 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.

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, gefitinib).

There is no evidence of an interaction between ranitidine and amoxicillin, 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

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. It is excreted in human breast milk.

Like other drugs it should only be used during pregnancy and breastfeeding if considered essential.

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 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 ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $\leq 1/100$), rare ($\geq 1/10,000$, $\leq 1/1000$), very rare ($\leq 1/10,000$),

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) following the parenteral and oral administration of ranitidine.

Very Rare: Anaphylactic shock

Unknown: Dyspnoea

These events have been reported after a single dose.

Psychiatric Disorders

Very Rare: Depression, Reversible mental confusion, and hallucinations.

These have been reported predominantly in severely ill, in the 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 H₂ receptor antagonists bradycardia, A-V Block, 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 System and Breast Disorders

Very Rare: Reversible impotence, breast symptoms and breast conditions (such as gynaecomastia and galactorrhoea)

No clinically significant interference with endocrine or gonadal function has been reported. There have been a few reports of breast symptoms (swelling and/or discomfort) in men taking ranitidine; some cases have resolved on continued ranitidine treatment. Discontinuation of therapy may be necessary in order to establish the underlying cause.

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 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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms

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. If need be, the drug may be removed from the plasma by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for Acid Related Disorders,

ATC Code: A02BA02

Ranitidine is a specific rapidly acting histamine H₂-antagonist. It inhibits basal and stimulated secretion of gastric acid, reducing both the volume and the acid and pepsin content of the secretion. Ranitidine 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 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.

Special Patient 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

Extensive studies in animals have not revealed any significant toxicological abnormalities nor any mutagenic potential of ranitidine. Chronic high dose tests in rodents have not demonstrated carcinogenicity.

Reproductive toxicological studies in rodents have not revealed any teratological or toxicological effects of ranitidine.

In standard bacterial tests for mutagenicity (Salmonella, E. Coli) at concentrations up to the maximum recommended for these assays ranitidine was not found to be mutagenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Magnesium Stearate

Hypromellose
Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Polyamide/Aluminium/PVC/Aluminium blisters containing 10 tablets. Blisters packaged into outer container to give total of 30, 60 or 100 tablets.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited
Unit 3, Canalside, Northbridge Road,
Berkhamsted, Herts, HP4 1EG
UK.

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0030

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06/03/2007

10 DATE OF REVISION OF THE TEXT

04/12/2015