RANITIDINE 150MG FILM COATED TABLETS
PL 17907/0029

RANITIDINE 300MG FILM COATED TABLETS
PL 17907/0030

UKPAR

TABLE OF CONTENTS

Lay Summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 12
Steps taken after authorisation – summary	Page 13
Summary of Product Characteristics	Page 14
Patient Information Leaflet	Page 31
Labelling	Page 35

RANITIDINE 150MG FILM COATED TABLETS
PL 17907/0029

RANITIDINE 300MG FILM COATED TABLETS
PL 17907/0030

LAY SUMMARY

The MHRA granted Bristol Laboratories Ltd Marketing Authorisations (licences) for the medicinal products Ranitidine 150mg film coated tablets (PL 17907/0029) and Ranitidine 300mg film coated tablets (PL 17907/0030). These are prescription only medicines (POM) for the prevention and treatment of ulcers in the stomach or duodenum; to treat ulcers associated with the germ *Helicobacter pylori* when used with antibiotics; to heal and prevent problems caused by acid in the oesophagus or too much acid in the stomach which can cause pain or discomfort sometimes known as indigestion, dyspepsia or heartburn; or before surgical operations for the prevention of acid coming up from the stomach during the anaesthetic.

Ranitidine 150mg and 300mg film coated tablets contain the active ingredient ranitidine which is a H_2-blocker that prevents your stomach from producing too much acid.

The test products were considered to be equivalent to the original products Zantac Tablets 150mg and 300mg (Glaxo Wellcome UK Ltd) based on the data submitted.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Ranitidine 150mg and 300mg film coated tablets outweigh the risks, hence Marketing Authorisations have been granted.

RANITIDINE 150MG FILM COATED TABLETS
PL 17907/0029

RANITIDINE 300MG FILM COATED TABLETS
PL 17907/0030

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 7
Clinical assessment (including statistical assessment)	Page 8
Overall conclusion and risk benefit assessment	Page 11

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Ranitidine 150mg and 300mg film coated tablets to Bristol Laboratories Ltd on 06 March 2007. The products are prescription only medicines.

Two strengths of ranitidine were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC as ammended, claiming to be generic products of Zantac Tablets 150mg and 300mg (Glaxo Wellcome UK Ltd). The reference products have been authorised in the UK since September 1981 and August 1984 respectively, and so the 10-year period of data exclusivity has expired.

The products contain the active ingredient ranitidine, as ranitidine hydrochloride, and are indicated for duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents; prevention of non-steroidal anti-inflammatory drug associated duodenal ulcers; treatment of duodenal ulcers associated with *Helicobacter pylori* infection; post-operative ulcer; oesophageal reflux disease including long-tern management of healed oesophagitis; symptomatic relief in gastro-oesophageal reflux disease; Zollinger-Ellison Syndrome; chronic episodic dyspepsia, characterised by pain (epigastric or retrosternal) which is related to meals or disturbs sleep but not associated with the above conditions; prophylaxis of gastrointestinal haemorrhage with bleeding peptic ulcers; and before general anaesthesia in patients at risk of acid aspiration (Mendelson's syndrome), particularly obstetric patients during labour.

Ranitidine is an H_2-receptor antagonist. It inhibits basal and stimulated secretion of gastric acid, reducing both the volume and the acid and pepsin content of the secretion.

Both applications were submitted at the same time and depend on the bioequivalence study that compares the applicant's products with the reference product Zantac Tablets 300mg (GlaxoSmithKline, UK). Consequently, all sections of the Scientific Discussion refer to both applications.

PHARMACEUTICAL ASSESSMENT

COMPOSITION

The products are formulated as film-coated tablets containing 150mg or 300mg of the active pharmaceutical ingredient ranitidine, as ranitidine hydrochloride. The excipients present are microcrystalline cellulose, magnesium stearate, hypromellose and titanium dioxide.

Ranitidine 150mg and 300mg film coated tablets are presented in aluminium-foil sealed polyamide/Aluminium/PVC blisters in packs of 30, 60 or 100 tablets.

DRUG SUBSTANCE

Ranitidine Hydrochloride

All aspects of the manufacture and control of ranitidine hydrochloride are supported by EDQM Certificates of Suitability. These certificates are accepted as confirmation of the suitability of ranitidine hydrochloride for inclusion in this medicinal product.

Stability data have been generated supporting a retest period of 2 years from one supplier and 3 years from the other supplier when stored in the proposed packaging.

DRUG PRODUCT

Other ingredients

All excipients used in the manufacture of the tablets are routinely tested for compliance with current relevant international standards.

Satisfactory certificates of analysis have been provided for all excipients.

No excipients used contain material of animal or human origin.

Dissolution profiles

Dissolution profiles for the drug products (Ranitidine 150mg and 300mg film coated tablets) were found to be similar to the reference products (Zantac Tablets 150mg and 300mg).

Impurity profiles

Data was provided for the drug product and reference product. No known or unknown impurities were detected.

Manufacture

A full description and a detailed flow-chart of the manufacturing method including in-process control steps has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of both strengths. The results are satisfactory.

Finished product specification
The proposed finished product specification is acceptable and the analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed release specification. Suitable reference standards were used.

Container Closure System
Satisfactory specifications and certificates of analysis have been provided for the packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability data support the proposed shelf-life of 2 years with storage conditions "Do not store above 25°C. Store in the original package."

Bioequivalence/bioavailability
Refer to the clinical assessment report.

SPC, PIL and Labels
The SPC, PIL and labels are pharmaceutically acceptable.

The marketing authorisation holder has provided a commitment to update the marketing authorisation with a patient information leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 01 July 2008.

CONCLUSION

The proposed products have been shown to be generic products of the reference products and have met the requirements with respect to qualitative and quantitative content of the active substance. Similar dissolution profiles have been demonstrated for the proposed and reference products.

It is recommended that Marketing Authorisations should be granted for these applications.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.

CLINICAL ASSESSMENT

INTRODUCTION AND BACKGROUND

These are generic abridged applications for film-coated tablets containing 150mg or 300mg ranitidine as ranitidine hydrochloride.

The applications are submitted under the provisions of Directive 2001/83/EC Article 10.1 as amended, claiming that Ranitidine 150mg and 300mg film coated tablets are generic products of Zantac Tablets 150mg and 300mg (Glaxo Wellcome UK Ltd) which have been authorised in the UK for more than 10 years.

Ranitidine is an H_2 antagonist gastric antisecretory drug and is well characterised in the literature.

INDICATIONS

The following indications have been approved:

Duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents.
Prevention of non-steroidal anti-inflammatory drug associated duodenal ulcers.
Treatment of duodenal ulcers associated with Helicobacter pylori infection.
Post-operative ulcer.
Oesophageal reflux disease including long-term management of healed oesophagitis.
Symptomatic relief in gastro-oesophageal reflux disease.
Zollinger-Ellison Syndrome.
Chronic episodic dyspepsia, characterised by pain (epigastric or retrosternal) which is related to meals or disturbs sleep but not associated with the above conditions.
Prophylaxis of gastrointestinal haemorrhage from stress ulceration in seriously ill patients.
Prophylaxis of recurrent haemorrhage with bleeding peptic ulcers.
Before general anaesthesia in patients at risk of acid aspiration (Mendelson's syndrome), particularly obstetric patients during labour.

DOSE AND DOSE SCHEDULE

The proposed dose and dose schedule for these products to be used for the above indications are consistent with those of the reference products.

PHARMACODYNAMICS

No new data were submitted. The pharmacodynamics of ranitidine are well described. It is a specific, rapidly acting histamine H_2-antagonist which inhibits basal and

stimulated secretion of gastric acid, reducing both the volume and the acid and pepsin content of the secretion.

PHARMACOKINETICS

No new data were submitted. The pharmacokinetics of ranitidine are well described. Absorption of ranitidine after oral administration is rapid and peak plasma concentrations are usually achieved within two hours of administration. Food or antacids do not significantly impair absorption and the expert report provides satisfactory reassurance that absorption is linear over the therapeutic range. The elimination half-life of ranitidine is approximately two hours. Ranitidine is excreted via the kidneys mainly as the free drug and, in minor amounts, as smaller quantities of S-oxide and desmethyl ranitidine. The 24 hour urinary recovery of free ranitidine and its metabolites is about 40% with orally administered drug.

BIOEQUIVALENCE

A single bioequivalence study was presented for the 300mg tablet, carried out in compliance with Good Clinical Practice.

The reference product used in the study was Zantac Tablets 300mg manufactured by GlaxoSmithKline, UK. The test product used was Ranitidine 300mg film coated tablets.

In this comparative, randomised, two-way, two-period, single dose crossover study, 24 healthy fasted male and female volunteers received 300mg orally of the applicant's test product and the reference product. Serum drug levels were measured hourly for the first 4 hours following dosing then at 6, 8, 10, 12 and 24 hours. The schedule was appropriate for accurate determination of AUC_{inf} but the hourly sampling interval around C_{max} is inadequate to estimate this parameter with any accuracy. The washout period of 7 days between phases was sufficiently long given the short half life of the drug (approximately 2.5 hours).

Results

No subjects discontinued the study. Data for AUC_t, AUC_{inf} and C_{max} were analysed by ANOVA. T_{max} was analysed non-parametrically. Bioequivalence results for test/reference ratios with 90% Confidence Intervals are as follows:

	Test	**Reference**	**Test/Reference ratio**
AUC_t	5727	5899	0.98 (0.86 – 1.04)
C_{max}	1177	1254	0.94 (0.81 – 1.08)
T_{max}	3.33 hrs	2.92 hrs	

The inability of the sampling interval to accurately estimate C_{max} is not considered to be a major deficiency as C_{max} is not a very important parameter for this drug and there is no indication that the two products performed significantly differently in their rate of absorption. Bioequivalence has been satisfactorily demonstrated for the 300mg preparation, in accordance with CPMP criteria. As the formulations for the two

strengths are linear and the products show comparable dissolution profiles, exemption for another bioequivalence study for the 150mg strength is justified.

CLINICAL EFFICACY

No new efficacy data were presented in these applications and none are required.

CLINICAL SAFETY

No new safety data were presented in these applications and none are required. There were no significant adverse events in the bioequivalence study and the literature review in the expert report did not identify any new safety issues.

CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified medical doctor. It is an adequate summary of the clinical data provided in the dossier.

SPC, PIL and LABELS

The SPC, PIL and labels are acceptable.

CONCLUSIONS

The clinical efficacy and safety of ranitidine is well known from its use in clinical practice. No new data were submitted and this is acceptable. Bioequivalence of the product has been shown. Considering the relative composition of the 150 and 300mg products, *in vitro* dissolution profiles and ranitidine pharmacokinetics, extrapolation of the outcome of the bioequivalence study to the lower strength product is justified. Marketing Authorisations should be granted for these applications.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Ranitidine 150mg and 300mg film coated tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Ranitidine 300mg film coated tablets and Zantac Tablets 300mg (GlaxoSmithKline, UK).

No new or unexpected safety concerns arise from these applications.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the reference products are interchangeable. The risk benefit is, therefore, considered to be positive.

RANITIDINE 150MG FILM COATED TABLETS
PL 17907/0029

RANITIDINE 300MG FILM COATED TABLETS
PL 17907/0030

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation applications on 24 June 2002.

2 Following standard checks and communication with the applicant, the MHRA considered the applications valid on 23 August 2002.

3 Following assessment of the applications, the MHRA requested further information relating to the quality dossiers on 10 January 2003, 27 June 2003, 04 August 2004, 22 December 2004, 21 August 2006 and 29 November 2006 and further information relating to the clinical dossiers on 10 January 2003.

4 The applicant responded to the MHRA's requests, providing further information on 28 March 2003, 23 April 2004, 14 September 2004, 28 November 2005, 29 November 2006 and 13 December 2006 for the quality sections, and again on 28 March 2003 for the clinical sections.

5 The applications were determined on 06 March 2007.

RANITIDINE 150MG FILM COATED TABLETS
PL 17907/0029

RANITIDINE 300MG FILM COATED TABLETS
PL 17907/0030

STEPS TAKEN AFTER AUTHORISATION – SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ranitidine 150mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film coated tablets.

White to almost white, circular, biconvex, film coated tablets embossed with “BL” on one side and “150” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents.

Prevention of non-steroidal anti-inflammatory drug associated duodenal ulcers.

Treatment of duodenal ulcers associated with *Helicobacter pylori* infection.

Post-operative ulcer.

Oesophageal reflux disease including long-term management of healed oesophagitis.

Symptomatic relief in gastro-oesophageal reflux disease.

Zollinger-Ellison Syndrome.

Chronic episodic dyspepsia, characterised by pain (epigastric or retrosternal) which is related to meals or disturbs sleep but not associated with the above conditions.

Prophyhlaxis of gastrointestinal haemorrhage from stress ulceration in seriously ill patients.

Prophylaxis of recurrent haemorrhage with bleeding peptic ulcers.

Before general anaesthesia in patients at risk of acid aspiration (Mendelson’s syndrome), particularly obstetric patients during labour.

4.2 Posology and method of administration

Adults :

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

Duogenal ulcer, gastric ulcer.

The standard dosage regimen is 150 mg twice daily or 300 mg at night. It is not necessary to time the dose in relation to meals.

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 of treatment in those not fully healed after the initial course of therapy.

Ulcers following NSAID therapy or associated with continued NSAID's

8 weeks treatment may be necessary.

Prevention of NSAID associated duodenal ulcers :

150mg twice daily may be given concomitantly with NSAID therapy.

In duodenal ulcer, 300mg 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 300mg at bedtime or 150mg twice daily may be given with oral amoxycillin 750 mg three times daily and metronidazole 500mg three times daily for two weeks. Therapy with ranitidine should continue for a further two weeks. This dose regimen signficantly reduces the frequency of duodenal ulcer recurrence.

Maintenance treatment at a reduced dosage of 150mg 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:

Symptom relief in gastro-oesophageal reflux disease. In patients with gastro-oesophageal reflux disease, a dose regimen of 150mg twice daily for 2 weeks is recommended and this can be repeated in patients in whom the initial symptomatic response is inadequate.

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 weeks or 12 weeks if necessary.

In patients with moderate to severe oesophagitis, the dosage of ranitidine may be increased to 150 mg 4 times daily for up to 12 weeks. The increased dose has not been associated with an increased incidence of unwanted effects.

Healed oesophagitis :

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

Zollinger-Ellison syndrome :

The starting dose for Zollinger-Ellison syndrome is 150 mg three times daily, and this may be increased as necessary. Doses up to 6 grams per day have been well tolerated.

Chronic episodic dyspepsia :

The standard dosage regimen for patients with chronic episodic dyspepsia is 150 mg twice daily for up to 6 weeks. Anyone not responding or relapsing shortly afterwards should be investigated.

Prophylaxis of haemorrhage from stress ulceratin in seriously ill patients or prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration.

150mg twice daily may be substituted for the injection once oral feeding commences.

Prophylaxis of acid aspiration (Mendelson's) syndrome :

150 mg oral dose can be given 2 hours before anaesthesia, and preferably also 150 mg the previous evening. Alternatively, the injection is also available. In obstetric patients in labour 150 mg every 6 hours, but if general anaesthesia is required it is recommended that a non-particulate antacid (e.g. sodim citrate) be given in addition. The usual precautions to avoid acid aspiration should also be taken.

Children :

The recommended oral dose for the treatment of peptic ulcer in children is 2 mg / kg to 4 mg / kg twice daily to a maximum of 300 mg ranitidine per day.

Renal impairement :

Accumulation of ranitidine with resulting elevated plasma concentrations will occur in patients with several renal impairement. 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, 150mg twice daily dosage should be instituted followed, if need be, by maintenance treatment of 150 mg at night.

4.3 Contraindications

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

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) 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 severe renal impairment. The dosage should be adjusted as detailed above under Dosage 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.

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

Use in elderly patients : 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.

4.5 Interaction with other medicinal products and other forms of interaction

Ranitidine does not inhibit the hepatic cytochrome P450-linked mixed function oxygenase system. Accordingly, ranitidine does not potentiate the actions of drugs which are inactivated by this enzyme; these include diazepam, lignocaine, phenytoin, propranolol, theophylline and warfarin. There is no evidence of an interaction between ranitidine and amoxycillin or metronidazole.

4.6 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.

Lactation :

It is excreted in human breast milk.

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

4.7 Effects on ability to drive and use machines

No known effect.

4.8 Undesirable effects

The following convention has been utilized 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).

Blood and the lymphatic 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.

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.

Reproductive System and Breast Disorders

Very Rare:

Reversible impotence. Breast symptoms in men.

4.9 Overdose

Ranitidine is very specific in action and accordingly no particular problems are expected following overdosage. 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

Ranitidine 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. 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 of ranitidine after oral administration is rapid and peak plasma concentrations are usually achieved within two hours of administration. Absorption is not significantly impaired by food or antacids. The elimination half-life of ranitidine is approximately 2 hours. Ranitidine is excreted via the kidneys mainly as the free drug and in minor amounts as metabolites. Its major metabolite is an N-oxide and there are smaller quantities of S-oxide and desmethyl ranitidine. The 24-hour urinary recovery of free ranitidine and its metabolites is about 40% with orally administered drug.

5.3 Preclinical safety data

No additional data of relevance.

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

2 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 17907/0029

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/03/2007

10 DATE OF REVISION OF THE TEXT

06/03/2007

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 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

4.2 Therapeutic indications

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.

4.2 Posology and method of administration

Adults: 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. 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.

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 nocte. The increased dose has not been associated with an increased incidence of unwanted effects.

For duodenal ulcers associated with *Helicobacter pylori* infection Rantidine 300 mg at bedtime or 150 mg twice daily may be given with oral amoxycillin 750 mg three times daily and metronidazole 500 mg three times daily for two weeks. Therapy with Rantidine 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.

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 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.

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 (see separate SPC) once oral feeding commences in patients considered to be still at risk from these conditions.

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: The recommended oral dose for treatment of peptic ulcer in children is 2 mg/kg to 4 mg/kg twice daily to a maximum of 300 mg ranitidine per day.

Renal Impairment:

Accumulation of ranitidine with resulting elevated plasma concentrations will occur in patients with severe renal impairment. 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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Treatment with a histamine H2-antagonist may mask symptoms associated with carcinoma of the stomach and may therefore delay diagnosis of the condition. Accordingly, where gastric ulcer has been diagnosed or in patients of middle age and over with new or recently changed dyspeptic symptoms the possibility of malignancy should be excluded before therapy with Rantidine Tablets is instituted.

Ranitidine is excreted via the kidney and so plasma levels of the drug are increased in patients with severe renal impairment. The dose should be adjusted as detailed above under Dosage in 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.

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:

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.

4.5 Interaction with other medicinal products and other forms of interaction

Ranitidine does not inhibit the hepatic cytochrome P450-linked mixed function oxygenase system. Accordingly, ranitidine does not potentiate the actions of drugs which are inactivated by this enzyme; these include diazepam, lignocaine, phenytoin, propranolol, theophylline and warfarin. There is no evidence of an interaction between ranitidine and amoxycillin or metronidazole.

4.6 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.

Lactation :

It is excreted in human breast milk.

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

4.7 Effects on ability to drive and use machines

No known effect.

4.9 Undesirable effects

The following convention has been utilized 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).

Blood and the lymphatic 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.

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.

Reproductive System and Breast Disorders

Very Rare:

Reversible impotence. Breast symptoms in men.

4.9 Overdose

Ranitidine is very specific in action and accordingly no particular problems are expected following overdosage. 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

Ranitidine 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. 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

The bioavailabililty of ranitidine is consistently about 50%. Absorption of ranitidine after oral administration is rapid and peak plasma concentrations are usually achieved within 2-3 hours of administration. Absorption is not significantly impaired by food or antacids. Ranitidine is not extensively metabolised. Elimination of the drug is primarily by tubular secretion. The elimination half-life of ranitidine is 2-3 hours. In balanced studies with 150 mg 3H-Ranitidine 60-70% of an oral dose was excreted in urine and 25% in faeces. Analysis of urine excretion in the first 24 hours after dosing showed that 35% of the oral dose was eliminated unchanged. About 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.

5.3 Preclinical safety data

No additional data of relevance.

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

2 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

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/03/2007

10 DATE OF REVISION OF THE TEXT

06/03/2007

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

Please read this entire leaflet carefully before you start taking this medicine.
Keep the leaflet; you may need to read it again.
This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
If you have any further questions, please ask your doctor or pharmacist.

The name of this medicine is
RANITIDINE 150 MG FILM COATED TABLETS

The tablets are film-coated and contain 150 mg of the active ingredient ranitidine hydrochloride. The tablets also contain microcrystalline cellulose, magnesium stearate Hypromellose and titanium dioxide (E171)
The product licence holder and manufacturer is Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG, UK.

What the tablets are and what they are used for

The tablets are white to almost white, circular, biconvex, film coated tablets embossed with “BL” on one side and “150” on the other.
Ranitidine 150 mg Film Coated Tablets comes in blister packs of 30, 60 or 100 tablets.
The active ingredient ranitidine belongs to a group of medicines called 'H2-blockers'. It works by preventing your stomach from producing too much acid. Ranitidine 150 mg Film Coated tablets are used:

- to heal and prevent ulcers in the stomach or, the part it empties into, the duodenum
- to clear up infection with the germ *Helicobacter pylori* when used with antibiotics
- to prevent ulcers from bleeding
- to heal and prevent problems caused by acid in the gullet (oesophagus) or too much acid in the stomach, which can cause pain or discomfort sometimes known as “indigestion”, “dyspepsia” or “heartburn”
- to prevent ulcers, which can be a side effect of some medicines used to treat arthritis
- before surgical operations, to prevent acid coming up from the stomach during the anaesthetic

If you are not sure why you are taking these tablets, ask your doctor.

Before taking your medicine

Please get your pharmacist or doctors' advice before taking these tablets if:

- you are allergic to any of the ingredients of Ranitidine 150 mg Tablets listed above
- you are pregnant, trying to become pregnant or breast feeding
- you suffer from a rare condition called porphyria
- you have been told that your kidneys are not working properly
- you are middle aged or older with new or recently changed indigestion symptoms
- you are taking any medicines, including 'pain killers' of the class known as non-steroidal anti-inflammatory drugs (NSAIDS, such as aspirin or ibuprofen) regularly. This advice is even more important if you are elderly.

Taking your medicine

Adults (including the elderly) and children 16 years of age and older:
The usual dose is one tablet in the morning and one in the evening.
Swallow each tablet whole with a drink of water.
If prescribed for a **child,** make sure the tablets are taken as the label says.

If you miss a dose:
If you forget to take a dose, take it as soon as you remember, then go on as before. Never double up on the next dose to make up for the one missed.

If you take too much:
If you have taken too many tablets, you must obtain immediate assistance from your doctor or hospital casualty department.

If your symptoms get worse or are no better with this medicine, please consult your doctor.

Possible Side -Effects

Most people taking Ranitidine 150mg Tablets find they cause them no problems.
As with all medicines some people may be allergic to them but this is very rare with Ranitidine 150 mg tablets.
The usual allergic reaction is a skin rash or sometimes swelling of the eyelids, face or lips and some people have noticed sudden wheeziness, pain or tightness of the chest or have felt faint feverish, or collapsed.
In this case stop taking the tablets and tell your doctor immediately.
Headaches, dizziness, hallucinations, depression, and confusion have been reported rarely. In addition, there have been rare reports of uncontrolled movements, this effect is usually reversible and should get better once you stop taking this medicine. Even more rarely the following have been reported in association with using the medicine:

- Aches and pains in muscles and joints
- Inflammation of the liver (with or without yellowing of the skin)
- Pancreatitis (stomach pain)
- Slow or irregular heart beat
- Inflammation of blood vessels (vasculitis)
- Hair loss (alopecia)
- Blurred vision

In men, breast tenderness and/ or breast enlargement; interference with sexual function (impotence) have been reported very rarely. This interference with sexual function is normally reversible and should get better once you stop taking this medicine.
The results of laboratory tests on your liver may be altered.
Tests sometimes show upsets to blood counts only very rarely causing unusual tiredness, shortness of breath or a tendency to bruise or get infections.
Sometimes your doctor may prescribe antibiotics which can cause diarrhoea.
If you feel unwell or have any unusual symptoms you do not understand, stop taking the tablets and tell your doctor or pharmacist.

Storing your medicine

Keep out of the reach and sight of children.
Do not store above 25°C. Store in the original package (blister carton) to protect from moisture.
Do not use the tablets after the expiry date shown on the carton.
REMEMBER this medicine has been prescribed for you. Do not give it to anyone else as it may harm them even if their symptoms appear to be the same.
If your doctor decides to stop treatment, return any left-over tablets to your pharmacist.
Only keep them if your doctor tells you to.
If you have any questions or are not sure about anything, ask your pharmacist or doctor.

This leaflet was last revised October 2005.

PATIENT INFORMATION LEAFLET

Please read this entire leaflet carefully before you start taking this medicine.
Keep the leaflet; you may need to read it again.
This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
If you have any further questions, please ask your doctor or pharmacist.

The name of this medicine is
RANITIDINE 300 MG FILM COATED TABLETS

The tablets are film-coated and contain 300 mg of the active ingredient ranitidine hydrochloride. The tablets also contain microcrystalline cellulose, magnesium stearate Hypromellose and titanium dioxide (E171)
The product licence holder and manufacturer is Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG, UK.

What the tablets are and what they are used for

The tablets are 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 side. Ranitidine 300 mg Film Coated Tablets comes in blister packs of 30, 60 or 100 tablets.
The active ingredient ranitidine belongs to a group of medicines called 'H2-blockers'. It works by preventing your stomach from producing too much acid. Ranitidine 300 mg Film Coated tablets are used:

- to heal and prevent ulcers in the stomach or, the part it empties into, the duodenum
- to clear up infection with the germ *Helicobacter pylori* when used with antibiotics
- to prevent ulcers from bleeding
- to heal and prevent problems caused by acid in the gullet (oesophagus) or too much acid in the stomach, which can cause pain or discomfort sometimes known as “indigestion”, “dyspepsia” or “heartburn”
- to prevent ulcers, which can be a side effect of some medicines used to treat arthritis
- before surgical operations, to prevent acid coming up from the stomach during the anaesthetic

If you are not sure why you are taking these tablets, ask your doctor.

Before taking your medicine

Please get your pharmacist or doctors’ advice before taking these tablets if:

- you are allergic to any of the ingredients of Ranitidine 300 mg Tablets listed above
- you are pregnant, trying to become pregnant or breast feeding
- you suffer from a rare condition called porphyria
- you have been told that your kidneys are not working properly
- you are middle aged or older with new or recently changed indigestion symptoms
- you are taking any medicines, including 'pain killers' of the class known as non-steroidal anti-inflammatory drugs (NSAIDS, such as aspirin or ibuprofen) regularly. This advice is even more important if you are elderly.

Taking your medicine

The usual dose is one tablet at night or up to one tablet twice a day.
Swallow each tablet whole with a drink of water.
If prescribed for a **child,** make sure the tablets are taken as the label says.

If you miss a dose:
If you forget to take a dose, take it as soon as you remember, then go on as before. Neverdouble up on the next dose to make up for the one missed.

If you take too much:
If you have taken too many tablets, you must obtain immediate assistance from your doctor or hospital casualty department.

If your symptoms get worse or are no better with this medicine, please consult your doctor.

Possible Side -Effects

Most people taking Ranitidine 300mg Tablets find they cause them no problems.
As with all medicines some people may be allergic to them but this is very rare with Ranitidine 300 mg tablets.
The usual allergic reaction is a skin rash or sometimes swelling of the eyelids, face or lips and some people have noticed sudden wheeziness, pain or tightness of the chest or have felt faint feverish, or collapsed.
In this case stop taking the tablets and tell your doctor immediately.
Headaches, dizziness, hallucinations, depression, and confusion have been reported rarely. In addition, there have been rare reports of uncontrolled movements, this effect is usually reversible and should get better once you stop taking this medicine. Even more rarely the following have been reported in association with using the medicine:

- Aches and pains in muscles and joints
- Inflammation of the liver (with or without yellowing of the skin)
- Pancreatitis (stomach pain)
- Slow or irregular heart beat
- Inflammation of blood vessels (vasculitis)
- Hair loss (alopecia)
- Blurred vision

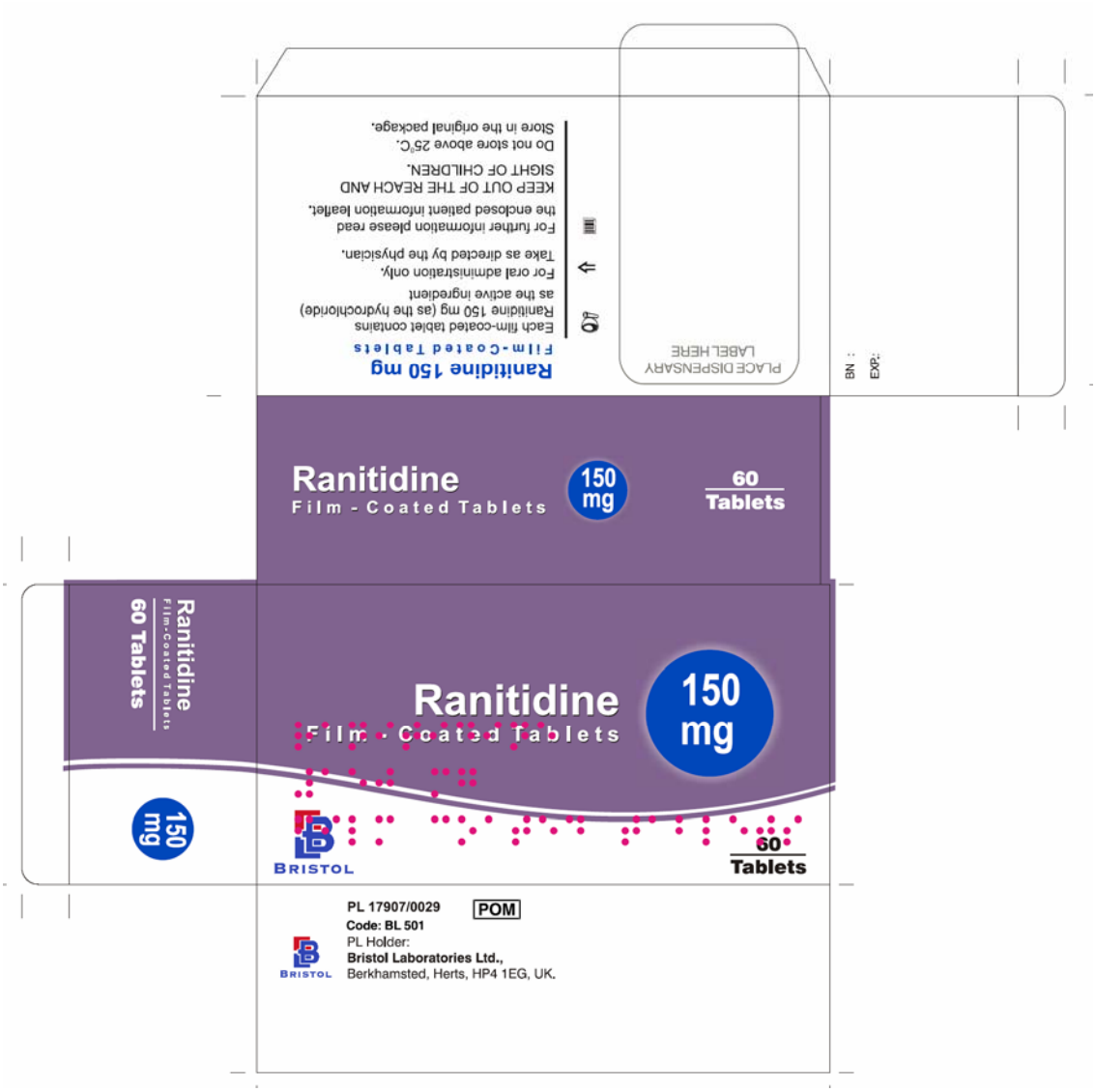
In men, breast tenderness and/ or breast enlargement; interference with sexual function (impotence) have been reported very rarely. This interference with sexual function is normally reversible and should get better once you stop taking this medicine.
The results of laboratory tests on your liver may be altered.
Tests sometimes show upsets to blood counts - only very rarely causing unusual tiredness, shortness of breath or a tendency to bruise or get infections.
Sometimes your doctor may prescribe antibiotics which can cause diarrhoea.
If you feel unwell or have any unusual symptoms you do not understand, stop taking the tablets and tell your doctor or pharmacist.

Storing your medicine

Keep out of the reach and sight of children.
Do not store above 25°C. Store in the original package (blister carton) to protect from moisture.
Do not use the tablets after the expiry date shown on the carton.
REMEMBER this medicine has been prescribed for you. Do not give it to anyone else as it may harm them even if their symptoms appear to be the same.
If your doctor decides to stop treatment, return any left-over tablets to your pharmacist.
Only keep them if your doctor tells you to.
If you have any questions or are not sure about anything, ask your pharmacist or doctor.

This leaflet was last revised October 2005.

LABELLING


Ranitidine
Film - Coated Tablets
150 mg
60 Tablets
Ranitidine
Film-Coated Tablets
60 Tablets
150 mg
BRISTOL
PL 17907/0029
POM
Code: BL 501
PL Holder:
Bristol Laboratories Ltd.,
Berkhamsted, Herts, HP4 1EG, UK.
PLACE DISPENSARY LABEL HERE
BN :
EXP:
Ranitidine 150 mg
Film-Coated Tablets
Each film-coated tablet contains
Ranitidine 150 mg (as the hydrochloride)
as the active ingredient
For oral administration only.
Take as directed by the physician.
For further information please read
the enclosed patient information leaflet.
KEEP OUT OF THE REACH AND
SIGHT OF CHILDREN.
Do not store above 25°C.
Store in the original package.


Ranitidine 150 mg
Film-coated tablet
Each film-coated tablet contains
Ranitidine 150 mg
(as the hydrochloride)
PL Holder
Bristol Laboratories Ltd.
Code: BL 501


PLACE DISPENSARY LABEL HERE
BN :
EXP:
Ranitidine 300 mg
Film-Coated Tablets
Each film-coated tablet contains
Ranitidine 300 mg (as the hydrochloride) as the active ingredient
For oral administration only.
Take as directed by the physician.
For further information please read the enclosed patient information leaflet.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Do not store above 25°C.
Store in the original package.
Ranitidine
Film - Coated Tablets
300 mg
30 Tablets
Ranitidine
Film-Coated Tablets
30 Tablets
300 mg
Ranitidine
Film - Coated Tablets
300 mg
BRISTOL
30 Tablets
PL 17907/0030
POM
Code: BL 501
PL Holder:
Bristol Laboratories Ltd.,
Berkhamsted, Herts, HP4 1EG, UK.


Ranitidine 300 mg
Film-coated tablet
Each film-coated tablet contains
Ranitidine 300 mg
(as the hydrochloride)
PL Holder
Bristol Laboratories Ltd.
Code: BL 501