

## Summary of Product Characteristics

### 1. Name of the medicinal product

Ranitidine Tablets BP 150 mg

### 2. Qualitative and quantitative composition

Each film coated tablet contains:

Ranitidine hydrochloride

equivalent to Ranitidine 150 mg

Excipients q.s.

Colour- sunset yellow lake

### 3. Pharmaceutical form

Tablet

### 4. Clinical particulars

#### 4.1 Therapeutic indications

*Adults*

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

Prevention of non-steroidal anti-inflammatory drug (NSAID) (including aspirin) associated duodenal ulcers, especially in patients with a history of peptic ulcer disease.

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.

*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)*

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

#### Duodenal 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 NSAIDs:

8 weeks treatment may be necessary

#### Prevention of NSAID associated duodenal ulcers:

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

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 two 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.

Gastro-oesophageal reflux disease:

Symptom relief in gastro-oesophageal reflux disease. In patients with gastro- oesophageal reflux disease, a dose regimen of 150 mg 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 300 mg 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 ulceration in seriously ill patients or prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration:

150 mg 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. sodium citrate) be given in addition. 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 30 kg of weight*

Pharmacokinetic properties (Other special populations)

*Patients over 50 years of age*

Pharmacokinetic properties (Other special 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 a duration of 4 weeks. For those patients with incomplete healing, another 4 weeks of therapy is indicated, as healing usually occurs after eight weeks of treatment.

Gastro-Oesophageal Reflux

The recommended oral dose for the treatment of gastro-oesophageal reflux in children is 5 mg/kg/day to 10 mg/kg/day administered as two divided doses to a maximum of 600 mg (the maximum dose is likely to apply to heavier children or adolescents with severe symptoms).

Neonates

Safety and efficacy in new-born patients has not been established.

Patients with renal impairment

Accumulation of ranitidine with resulting elevated plasma concentrations will occur in patients with renal impairment (creatinine clearance less than 50 ml/min).

Accordingly, it is recommended that the daily dose of ranitidine in such patients 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**

For oral administration.

### **4.3 Contraindications**

Hypersensitivity to the active substance(s) or to any of the excipients.

### **4.4 Special warnings and precautions for use**

#### *Malignancy*

The possibility of malignancy should be excluded before commencement of therapy in patients with gastric ulcer and in patients of middle age and over with new or recently changed dyspeptic symptoms as treatment with ranitidine may mask symptoms of gastric carcinoma.

#### *Renal Disease*

Ranitidine is excreted via the kidney and so plasma levels of the drug are increased in patients with renal impairment. The dosage should be adjusted with patients 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.

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 .

### **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).

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

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

## 4.6 Fertility, pregnancy and lactation

### *Pregnancy*

Ranitidine crosses the placenta but therapeutic doses administered to obstetric patients in labour or undergoing caesarean section have been without any adverse effect on labour, delivery or subsequent neonatal progress. Like other drugs, ranitidine should only be used during pregnancy if considered essential.

### *Breast-feeding*

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

### *Fertility*

There are no data on the effects of ranitidine on human fertility. There were no effects on male and female fertility in animal studies.

## 4.7 Effects on ability to drive and use machines

None reported.

## 4.8 Undesirable effects

The following convention has been utilised for the classification of undesirable effects: very common ( $\geq 1/10$ ), 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 post-marketing data.

### *Blood & Lymphatic System Disorders*

Very Rare: Blood count changes (leucopenia, thrombocytopenia). These are usually reversible. Agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or marrow aplasia.

### *Immune System Disorders*

Rare: Hypersensitivity reactions (urticaria, angioneurotic oedema, fever, bronchospasm, hypotension and chest pain).

Very Rare: Anaphylactic shock.

Not known: Dyspnoea.

These events have been reported after a single dose.

#### *Psychiatric Disorders*

Very Rare: Reversible mental confusion, depression and hallucinations.

These have been reported predominantly in severely ill patients, in elderly and in nephropatic patients.

#### *Nervous System Disorders*

Very Rare: Headache (sometimes severe), dizziness and reversible involuntary movement disorders.

#### *Eye Disorders*

Very Rare: Reversible blurred vision.

There have been reports of blurred vision, which is suggestive of a change in accommodation.

#### *Cardiac Disorders*

Very Rare: As with other H<sub>2</sub> receptor antagonists bradycardia, A-V block and tachycardia.

#### *Vascular Disorders*

Very Rare: Vasculitis.

#### *Gastrointestinal Disorders*

Uncommon: Abdominal pain, constipation, nausea (these symptoms mostly improved during continued treatment).

Very Rare: Acute pancreatitis, diarrhoea

#### *Hepatobiliary Disorders*

Rare: Transient and reversible changes in liver function tests.

Very Rare: Hepatitis (hepatocellular, hepatocanalicular or mixed) with or without jaundice, these were usually reversible.

#### *Skin and Subcutaneous Tissue Disorders*

Rare: Skin Rash.

Very Rare: Erythema multiforme, alopecia.

#### *Musculoskeletal and Connective Tissue Disorders*

Very Rare: Musculoskeletal symptoms such as arthralgia and myalgia.

#### *Renal and Urinary Disorders*

Rare: Elevation of plasma creatinine (usually slight; normalized during continued treatment)

Very Rare: Acute interstitial nephritis.

#### *Reproductive System and Breast Disorders*

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

#### *Paediatric population*

The safety of ranitidine has been assessed in children aged 0 to 16 years with acid-related disease and was generally well tolerated with an adverse event profile resembling that in adults. There are limited long term data available, in particular regarding growth and development.

### **4.9 Overdose**

#### *Symptoms and signs*

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

#### *Treatment*

Symptomatic and supportive therapy should be given as appropriate.

## **5. Pharmacological properties**

### **5.1 Pharmacodynamic properties**

Ranitidine is a specific rapidly acting histamine H<sub>2</sub>-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.

### Other special 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.

#### *Patients over 50 years of age*

In patients over 50 years of age, half-life is prolonged (3-4 h) and clearance is reduced, consistent with the age-related decline of renal function. However, systemic exposure and accumulation are 50% higher. This difference exceeds the effect of declining renal function, and indicates increased bioavailability in older patients.

### **5.3 Preclinical safety data**

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Magnesium stearate, Sodium starch glycolate(Primojel), Croscarmellose sodium (Primellsoe), Purified Talc, Microcrystalline cellulose PH 102 , Microcrystalline cellulose Plain ,Colloidal anhydrous silica , Instacoat (IC-MS-2398),Isopropyl alcohol , Dichloromethane,Film coat universal sunset yellow lake .

### **6.2 Incompatibilities**

None known

### **6.3 Shelf life**

24 Months

### **6.4 Special precautions for storage**

Store below 30°C. Store in the original package.  
KEEP OUT OF THE REACH OF CHILDREN.

### **6.5 Nature and contents of container**

Alu Alu strips of 20 tablets are packed in a mono carton and such 10 mono cartons are packed in an Outer carton along with package insert.

### **6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.



- 7. Marketing authorisation holder**  
Not Applicable
- 8. Marketing authorisation number(s)**  
Not Applicable
- 9. Date of first authorisation/renewal of the authorisation**  
Not Applicable
- 10. Date of revision of the text**  
Not Applicable