**Summary of Product Characteristics**

## 1. NAME OF THE MEDICINAL PRODUCT

Ranitidine 150 mg Effervescent Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 150 mg Ranitidine (as hydrochloride).

Excipients with known effect:
Each effervescent tablet contains 438 mg lactose monohydrate and 120 mg sodium.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Effervescent tablet.
Yellow-white to light-yellow cylindrical effervescent tablets with bevelled edges.

## CLINICAL PARTICULARS

### 4.1 Therapeutic indications

For the treatment of diseases of the upper gastro-intestinal tract, in which a reduction of gastric acid secretion is indicated:

Adults
- Duodenal ulcer
- Benign gastric ulcer
- Long-term treatment of duodenal ulcers to prevent their recurrence. Long-term treatment is indicated in patients with a history of recurrent ulcer
- Reflux oesophagitis
- Zollinger-Ellison syndrome.

Ranitidine is not indicated for the treatment of minor gastrointestinal complaints, such as a nervous stomach.

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

**For adults with normal renal function, the following dosing guidelines apply:**

*Duodenal and benign gastric ulcers*
2 effervescent tablets ranitidine 150 mg (= 300 mg ranitidine) after supper or at bedtime. Alternatively, 1 effervescent tablet Ranitidine 150 mg twice daily, taken in the morning and evening.
The therapy should last for four weeks. In the occasional patient in whom the ulcer is not fully healed after four weeks treatment, the treatment should be continued for a further four weeks at the same dose.

*Duodenal ulcers long term treatment*
Patients, who have responded to such short-term treatment, and only those with a history of recurrent ulcer, may if necessary continue treatment for up to 12 months with 1 effervescent tablet of Ranitidine 150 mg daily at bedtime, for *prophylaxis of recurrence.* Patients should undergo regular endoscopic examination.

For *reflux oesophagitis,* 2 effervescent tablets Ranitidine 150 mg (= 300 mg Ranitidine) after supper or at bedtime. Alternatively 1 effervescent tablet Ranitidine 150 mg twice daily (if necessary 4 times daily = 600 mg Ranitidine/day), taken in the morning and evening, for up to 8 weeks (12 weeks if necessary).

*Patients with very high gastric acid secretion, e.g. Zollinger-Ellison syndrome,* should initially receive treatment with 1 effervescent tablet ranitidine 150 mg three times daily (= 450 mg ranitidine daily). If necessary, the dose may be increased to 4-6 effervescent tablets ranitidine 150 mg daily (=600-900 mg ranitidine daily).
Patients may be stabilised on higher doses if measurement of gastric acid secretion demonstrates this to be necessary. Daily doses of up to 6 g Ranitidine have been given.

Doses may be administered irrespective of mealtimes.

**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**
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).

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

**Dosage guide for patients with renal impairment**
Depending on the creatinine clearance (ml/min) or serum creatinine level (mg/100 ml), the following dosages are recommended:

| Creatinine clearance (ml/min) | Serum creatinine (approx.)* (mg/100 ml) | Daily dose (oral) |
|---|---|---|
| Up to 30 | Over 2.6 | 150 mg ranitidine |
| Over 30 | Under 2.6 | 300 mg ranitidine |

* *The serum creatinine values are guidelines, which do not represent the same level of impairment for all patients with reduced kidney function. This is especially the case in elderly patients in whom there is an overestimation of kidney function through the serum creatinine concentration.*

The following formula can be used to estimate creatinine clearance from the measured serum creatinine (mg/100 ml), age (in years) and body weight (in kg). For women, the result needs to be multiplied by the factor 0.85.

$$\text{Creatinine clearance (ml/min)} = \frac{(140-\text{age}) \times \text{body weight}}{72 \times \text{serum creatinine}}$$

Ranitidine is dialysable. Haemodialysis reduces blood Ranitidine levels. Thus, dialysis patients should receive the above dose of Ranitidine after completion of dialysis.

**Method of administration**
Dissolve an effervescent tablet in a glass of water. Do not break the effervescent tablet. Wait until the effervescent tablet has been completely dissolved and drink the solution directly.

## 4.3 Contraindications

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

## 4.4 Special warning and precautions for use

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

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 section 4.2 under Dosage guide for patients with renal impairment.

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).

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.

Patients with peptic ulcers should be tested for the presence of *H. pylori*. If they are found positive an adequate eradication regimen should be given.

Caution should be observed in patients with severe hepatic dysfunction since ranitidine is metabolised in liver.

**Excipients**

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
Ranitidine 150 mg effervescent tablets contain 120 mg sodium per tablet, equivalent to 6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

The maximum daily dose of Ranitidine effervescent tablets for the treatment of reflux oesophagitis is equivalent to 24% of the WHO recommended maximum daily intake for sodium.

The maximum daily dose of Ranitidine effervescent tablets for the treatment of very high gastric acid secretion, e.g. Zollinger-Ellison syndrome, is equivalent to 36% of the WHO recommended maximum daily intake for sodium.

Ranitidine effervescent tablets is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

## 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 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, gefitnib).

Concomitant administration of 300 mg ranitidine and erlotinib decreased erlotinib exposure [AUC] and maximum concentrations [$C_{max}$] by 33% and 54%, respectively. However, when erlotinib was dosed in a staggered manner 2 hours before or 10 hours after ranitidine 150 mg b.i.d., erlotinib exposure [AUC] and maximum concentrations [$C_{max}$] decreased only by 15% and 17%, respectively.

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

Ranitidine may increase the effects of alcohol.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
Ranitidine crosses the placenta. 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 (see section 5.3).

## 4.7 Effects on the ability to drive and use machines

No effects on the ability to drive and use machines were reported when using ranitidine.

The effects of small amounts of alcohol may increase when taken together with Ranitidine effervescent tablets (see section 4.5). Under these circumstances the ability to react as well as the power of judgment may be reduced, thus impairing the ability to drive and the ability to operate machinery.

## 4.8 Undesirable effects

The following convention has been utilised for the classification of undesirable effects: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from available data)

Adverse event frequencies have been estimated from spontaneous reports from post-marketing data.

Blood and 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

Psychiatric disorders
*Very rare*
Reversible mental confusion, depression and hallucinations.
These have been reported predominantly in severely ill patients, in elderly patients and in nephropatic patients.

Nervous system disorders
*Uncommon*:
Fatigue

*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 tachycardia, bradycardia and AV-block

Vascular disorders
*Very Rare:*
Vasculitis

Respiratory, thoracic and mediastinal disorders
*Not known*
Pneumonia (see section 4.4)

Gastrointestinal disorders
*Uncommon*
Abdominal pain, diarrhoea, constipation, nausea (these symptoms mostly improved during continued treatment)

*Very rare*
Acute pancreatitis

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, pruritis.

*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; normalised 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 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 or search for MHRA Yellow Card in the Google Play or Apple App Store

### 4.9 Overdose

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

Treatment
Symptomatic and supportive therapy should be given as appropriate.

## PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: $H_2$-receptor antagonist, ATC-code: A02B A02.

Ranitidine is a competitive histamine $H_2$ -receptor antagonist. It inhibits basal gastric secretion and gastric secretion stimulated e.g. by histamine, pentagastrin and food. Ranitidine decreases both the acid content and also to a smaller extent the pepsin content and volume of the gastric juice.

In two studies using therapeutic doses of ranitidine 150 mg twice daily, gastric acid secretion was reduced by a mean of 63% and 69% respectively over 24 hours, with reductions of 73% and 90% respectively in nocturnal acid secretion. In two studies using the dosage recommended for prophylaxis of recurrence (150 mg nocte) Ranitidine produced mean reductions in gastric acid secretion of 42% and 69% respectively within 24 hours.
The gastric acid secretion was reduced by a mean of 50 to 60% within 24 hours after administration of therapeutic doses of 300 mg Ranitidine nocte, while the nocturnal acid secretion was reduced by approximately 90%.

## 5.2 Pharmacokinetic properties

Absorption
Ranitidine is rapidly absorbed after oral administration and attains peak blood concentrations after a mean of 1.25 – 3 hours. The mean bioavailability of Ranitidine in tablet form is approx. 50 % but inter-individual variation in bioavailability is wide, being quoted as 28 – 76 % in one study.

Distribution
Plasma protein binding is approx. 15%. The apparent distribution volume in adults is 1.2-1.8 l/kg and in children 2.5 l/kg.

After oral ingestion of 150 mg ranitidine as tablet, peak plasma levels of around 400 ng/ml were attained, with wide-individual variation. At twelve hours, mean plasma levels were still approx. 40 ng/ml. After administration of 300 mg ranitidine, peak plasma levels of approx. 700–800 ng/ml were attained.

The plasma concentration required for 50% inhibition of acid secretion in adults averaged 73-165 ng/ml in a number of studies.

To a very small extent, Ranitidine passes into the cerebrospinal fluid.

Biotransformation
Ranitidine is metabolised in the liver to ranitidine-N-oxide, N-desmethyl ranitidine, ranitidine-S-oxide and the furane acid analogue.

Elimination
Measurements of total clearance yielded mean values of 570-710 ml/min in adults. In children and adolescents a total clearance of almost 800 ml/min/1.73 $m^2$ was found, with a wide degree of scatter.

After oral administration, ranitidine is excreted within 24 hours via the kidneys to approx. 30% as unchanged ranitidine, up to 6% as N-oxide, to a small degree in demethylised and in S-oxidised form, and as furane acid analogue. In patients with sound kidneys, renal excretion is effected predominantly by tubular secretion with a renal clearance of about 490-520 ml/min. Additionally, ranitidine is excreted via the bile.

Special patient population

*Patients with renal impairment*
After oral intake, mean elimination half-life in patients with sound kidneys is 2.3-3 hours. In patients with renal insufficiency, the half-life is prolonged two to threefold.

*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 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tartaric acid
Sodium hydrogen carbonate
Lactose monohydrate
Povidone
Riboflavin 5´-phosphate sodium (E101)
Simethicone emulsion (contains simethicone, methylcellulose, sorbic acid and purified water)
Sodium cyclamate
Saccharin sodium
Lemon flavour H&R 290252 (contains citral, citronella oil, coriander oil, lime and acacia)
Macrogol 6000
Sodium hydroxide

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf-life

3 years.

### 6.4 Special precautions for storage

Do not store above 30°C. Keep the container tightly closed.

### 6.5 Nature and contents of container

Polypropylene container with LDPE cap. A quantity of desiccant (silicagel zeolite) is incorporated into the cap.
Pack sizes: 10, 20, 30, 50, 60, 90 or 100 effervescent tablets.

Not all pack sizes may be marketed

### 6.6 Special precautions for disposal

No special requirements.

## 7. MARKETING AUTHORIZATION HOLDER

Ratiopharm GmbH
Graf-Arco-Str. 3
89079 Ulm
Germany

## 8. MARKETING AUTHORIZATION NUMBER

PL 15773/0066

## 9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

23rd August 2002

## 10. DATE OF REVISION OF THE TEXT

10 November 2019