

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Ranitidine 30mg/ml Oral Solution

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of oral solution contains Ranitidine 30.0 mg (as hydrochloride).

Excipients with known effect:

Each 5ml of the oral solution contains:

550 mg sorbitol

400 mg ethanol 96%

18.45 mg sodium

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Oral Solution

Ranitidine 30mg/ml Oral Solution is a clear, yellowish orange solution with characteristic fruit odour.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Adults

Ranitidine Oral Solution is indicated for the treatment of duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents. In addition, Ranitidine Oral Solution is indicated for the prevention of NSAID associated duodenal ulcers. Ranitidine Oral Solution is also indicated for the treatment of post-operative ulcer, Zollinger-Ellison Syndrome and oesophageal reflux disease including long term management of healed oesophagitis. Other patients with 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 Oral Solution is indicated for the following conditions where reduction of gastric secretion and acid output is desirable; the prophylaxis of gastro-intestinal haemorrhage from stress ulceration in seriously ill patients, the prophylaxis of recurrent haemorrhage in patients with bleeding peptic ulcers and before general anaesthesia in patients considered to be at risk of acid aspiration (Mendelson's Syndrome), particularly obstetric patients during labour. For appropriate cases Ranitidine injection is also available (see separate SPC).

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.

See section 4.4 Special warnings and precautions for use.

## **4.2 Posology and method of administration**

Posology

**Adults (including the elderly)**

The usual dosage is 150 mg (5 ml) 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 300mg (10ml). 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 4 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, 8 weeks treatment may be necessary.

For the prevention of non-steroidal anti-inflammatory drug associated duodenal ulcers ranitidine 150 mg (5ml) twice daily may be given concomitantly with non-steroidal anti-inflammatory drug therapy.

In duodenal ulcer 300mg (10ml) twice daily for 4 weeks results in healing rates which are higher than those at 4 weeks with ranitidine 150 mg (5ml) twice daily or 300mg (10 ml) nocte. The increased dose has not been associated with an increased incidence of unwanted effects.

Maintenance treatment at a reduced dosage of 150 mg (5ml) 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:*

In the management of oesophageal reflux disease, the recommended course of treatment is either 150 mg (5ml) twice daily or 300mg (10ml) at bedtime for up to 8 weeks or if necessary 12 weeks.

In patients with moderate to severe oesophagitis, the dosage of ranitidine may be increased to 150 mg (5ml) four times daily for up to twelve weeks. The increased dose has not been associated with an incidence of unwanted effects.

For the long-term management of oesophagitis the recommended adult oral dose is 150 mg (5ml) twice daily. Long-term treatment is not indicated in the management of patients with unhealed oesophagitis with or without Barrett's epithelium.

*Zollinger-Ellison syndrome:*

In patients with Zollinger-Ellison Syndrome, the starting dose is 150 mg (5ml) three times daily and this may be increased as necessary. Patients with this syndrome have been given increasing doses up to 6 g (200 ml) 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 (5ml) twice daily for up to six weeks. Anyone not responding or relapsing shortly afterwards should be investigated.

*Prophylaxis of haemorrhage from stress ulceration or recurrent haemorrhage:*

In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients or in the prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration, treatment with ranitidine tablets 150 mgs 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 Mendelson's syndrome:*

In patients thought to be at risk of acid aspiration syndrome an oral dose of 150mg (5ml) can be given 2 hours before induction of general anaesthesia, and preferably also 150 mg (5ml) the previous evening.

In obstetric patients at commencement of labour, an oral dose of 150 mg (5ml) may be given followed by 150 mg (5ml) 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 (eg 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 dose is given.

#### Children (3 to 11 years)

See section 5.2 Pharmacokinetic properties (Other special populations)

Ranitidine Oral Solution contains approximately 7.5% w/v ethanol. Therefore an alternative formulation of ranitidine may be considered necessary for at-risk groups, including children (see section 4.4 Special warnings and precautions for use).

#### Patients over 50 years of age

See Section 5.2 Pharmacokinetic properties (Other special 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 300mg (10ml) 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 5mg/kg/day to 10mg/kg/day administered as two divided doses to a maximum of 600mg (20ml) (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 50ml/min). Accordingly, it is recommended that the daily dose of ranitidine in such patients be 150 mg (5ml) at night for 4 to 8 weeks. The same dose should be used for maintenance treatment if necessary. If an ulcer has not healed after treatment, the standard dosage regimen of 150mg (5ml) twice daily should be instituted, followed, if need be, by maintenance treatment at 150 mg (5ml) at night.

#### Method of administration

For oral administration

### **4.3 Contraindications**

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

### **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 as detailed in section 4.2 Patients with 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.

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

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.

Ranitidine Oral Solution contains approximately 7.5% w/v ethanol (alcohol), i.e. up to 200 mg per 2.5 ml which is equivalent to about 5.5 ml of beer or 2.5 ml of wine. It is harmful for those suffering from alcoholism. It should be taken into account in pregnant or lactating women, high-risk groups (those suffering from alcoholism, liver disease, epilepsy, brain injury or disease) and children (see section 4.2). It may modify or increase the effects of other medicines.

This product also contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Alternative formulation of ranitidine may be considered preferential in these populations.

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**

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 metronizadole.

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 Oral Solution 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.

### Breastfeeding

Ranitidine Oral Solution 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 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 nephropathic 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; 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 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](http://www.mhra.gov.uk/yellowcard).

## **4.9 Overdose**

### **Symptoms and signs**

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.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: H2-receptor antagonists

ATC code: A02BA02

#### **Mechanism of action**

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

the secretion. Ranitidine has a relatively long duration of action and a single 150 mg dose effectively suppresses gastric acid secretion for twelve hours.

## 5.2 Pharmacokinetic properties

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 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**

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**

Liquid Sorbitol 70% (E420)  
Ethanol 96%  
Disodium hydrogen phosphate anhydrous  
Sodium dihydrogen phosphate monohydrate  
Hydroxyethylcellulose  
Tutti frutti flavour  
Sodium saccharin  
Sucralose  
Sodium hydroxide solution 1.0N  
Purified water

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years  
After first opening of the bottle: 2 months

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

Store below 25°C.

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

Ranitidine 30mg/ml Oral Solution is filled into type III, amber, glass bottle of 150ml nominal capacity suitable for pharmaceutical solutions containing 150ml of drug product. A child-resistant HDPE screw cap with PEBD seal and tamper evident closure constitutes integral part of the primary container.

A 5 ml, CE marked LDPE oral syringe with 0.1 ml increments is also provided.

#### **6.6 Special precautions for disposal**

None.

### **7 MARKETING AUTHORISATION HOLDER**

Zentiva Pharma UK Limited  
12 New Fetter Lane  
London  
EC4A 1JP  
United Kingdom

### **8 MARKETING AUTHORISATION NUMBER(S)**

PL 17780/1000

### **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

09/09/2016

**10 DATE OF REVISION OF THE TEXT**

31/08/2020