Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ranitidine 150 mg/10 ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ranitidine Hydrochloride 167.5mg/10ml (equivalent to Ranitidine 150mg/10ml)

Ethanol = 810mg/10ml
Sorbitol = 1.4g/10ml
Sodium = 22 mg/10 ml

For full list of excipients see Section 6.1

3 PHARMACEUTICAL FORM

Oral Solution

A straw coloured liquid with odour of mint

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ranitidine is indicated for the treatment of duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents. In addition, ranitidine is indicated for the prevention of NSAID (including aspirin) associated duodenal ulcers.

Ranitidine is also indicated for the treatment of post-operative ulcer, Zollinger-Ellison Syndrome and treatment of oesophageal reflux disease including prevention of relapse.

Ranitidine 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
- before general anaesthesia in patients considered to be at risk of acid aspiration (Mendelson's Syndrome), particularly obstetric patients during labour.

Children (3 to 18 years)
- Short term treatment of peptic ulcer
- Treatment of gastro-oesophageal reflux, including reflux oesophagitis and symptomatic relief of gastro-oesophageal reflux disease.

See section 4.4. Special warnings and precautions for use.

4.2 Posology and method of administration

Posology

Adults (including the elderly):
Treatment of duodenal and gastric ulcer:
The usual dosage is 150mg twice daily, taken in the morning and evening or a single bedtime dose of 300mg. It is not necessary to time the dose in relation to meals. This may be increased to ranitidine 300mg twice daily without an increased incidence of unwanted effects.

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 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.

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.

Treatment of ulcers following NSAID therapy or associated with continuing NSAIDS
In ulcers following non-steroidal anti-inflammatory drug therapy or associated with continued non-steroidal anti-inflammatory drugs, eight weeks treatment may be necessary with 150mg bd or 300mg nocte.

Prevention of NSAID induced ulcers:
For the prevention of non-steroidal anti-inflammatory drug associated duodenal ulcers, ranitidine 150mg twice daily may be given concomitantly with non-steroidal anti-inflammatory drug therapy.

Treatment of oesophageal reflux disease including prevention of relapse:
In the management of oesophageal reflux disease, the recommended course of treatment is either 150mg twice daily or 300mg at bedtime for up to eight weeks or if necessary twelve weeks.

In patients with moderate to severe oesophagitis, the dosage of ranitidine may be increased to 150mg 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 150mg twice daily. Ranitidine is not indicated in patients with complications of reflux oesophagitis e.g. oesophageal stricture or Barrett's oesophagous.

In keeping with the recommended clinical practice, it is advisable that patients on long term maintenance therapy receive regular routine assessments by their practitioner (see Section 4.4)

Treatment of Zollinger-Ellison Syndrome:
In patients with Zollinger-Ellison Syndrome, the starting dose is 150mg three times daily and this may be increased as necessary. Patients with this syndrome have been given increasing doses up to 6g per day and these doses have been well tolerated.

Prophylaxis of haemorrhage from stress ulceration in seriously ill patients or prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration:
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 150mg/10ml Oral Solution b.d. may be substituted for Ranitidine Injection once oral feeding commences in patients considered to still be at risk from these conditions.

Prophylaxis of acid aspiration (Mendelson's Syndrome)
In patients thought to be at risk of acid aspiration syndrome an oral dose of 150mg can be given two hours before induction of general anaesthesia and preferably also 150mg the previous evening.

In obstetric patients at commencement of labour, an oral dose of 150mg may be given followed by 150mg 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.

Renal Insufficiency
Accumulation of ranitidine with resulting elevated plasma concentration will occur in patients with severe renal impairment (creatinine clearance less than 50 ml/min). Accordingly, it is recommended that the daily dose of ranitidine in such patients should be 150mg 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, the standard dosage regimen of 150 mg twice daily should be instituted, followed, if need be, by maintenance treatment at 150 mg at night.

<u>Children (3 to 11 years)</u>

See Section 5.2 Pharmacokinetic Properties - Special Patient Populations.

Ranitidine syrup contains 8%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).

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).

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

Method of administration
For oral administration

4.3 Contraindications

Known hypersensitivity to ranitidine or any of the excipients in the formulation.

4.4 Special warnings and precautions for use

Treatment with a histamine H_2-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 by endoscopy and biopsy before therapy with ranitidine is instituted.

In keeping with the recommended clinical practice, it is advisable that patients on long term maintenance therapy receive regular routine assessments by their practitioner (see Section 4.2)

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 in Section 4.2 under 'Renal Insufficiency'.

Regular supervision of patients who are taking non-steroidal anti-inflammatory drugs concomitantly with ranitidine is recommended, especially in the elderly and those with a history of peptic ulcer. Current evidence shows that ranitidine protects against NSAID associated ulceration in the duodenum and not in the stomach.

Patients on prolonged treatment (particularly more than one year) should be kept under regular surveillance.

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.

Rates of healing 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.

Physicians should be aware that on rare occasions immune system reactions (rash and hypereosinophilia) have been reported on reintroduction of ranitidine, even months or years after withdrawal.

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 H_2 receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk increase of 1.82 (95% CI 1.26 – 2.64).

Excipient Information

Ethanol – This product contains 8%w/v ethanol (alcohol), i.e. up to 405mg per 5ml spoonful which is equivalent to about 11ml of beer or 5ml of wine.
It is harmful for those suffering from alcoholism. It should be taken into account in pregnant or lactating women, children (see section 4.2) and high risk groups (those suffering from alcoholism, liver disease, epilepsy, brain injury or disease). It may modify or increase the effect of other medicines. The amount of alcohol in this medicinal product may impair the ability to drive or use machines (see Section 4.7).

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

Sorbitol – The product contains 700mg per 5ml spoonful of sorbitol which is a source of 175mg fructose. Patients with rare hereditary problems of fructose intolerance should not take this medicine. It can also cause stomach upset and diarrhoea in large amounts.

Sodium –The product contains 11mg of sodium per 5ml spoonful.

4.5 Interaction with other medicinal products and other forms of interactions

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 action 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, raltegravir) or a decrease in absorption (e.g. ketoconazole, itraconazole, atazanavir, delavirdine, gefitinib, lapatinib, cefpodoxime).

There is no evidence of an interaction between ranitidine and amoxicillin and metronidazole. If high doses (2g) 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.

4) Erlotinib and medicinal products altering pH

Concomitant administration of 300 mg ranitidine and erlotinib decreased erlotinib exposure [AUC] and maximum concentrations [Cmax] 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 [Cmax] decreased only by 15% and 17%, respectively.

4.6 Fertility, pregnancy and lactation

Ranitidine should not be administered during pregnancy or lactation unless considered essential by the physician.

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. Ranitidine is also excreted in human breast milk. Like other drugs, ranitidine should only be used during pregnancy and nursing if considered essential.

4.7 Effects on ability to drive and use machines

The amount of alcohol in this medicinal product may impair the ability to drive or use machines (see Section 4.4).

4.8 Undesirable effects

The following convention has been utilised 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). Adverse event frequencies have been estimated from spontaneous reports from post-marketing data.

Blood and the Lymphatic System Disorders
Very Rare:
Blood count changes (leucopenia, thrombocytopenia). These are usually reversible. Agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or marrow aplasia.
Not known:
Acute porphyria

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 (especially in the elderly or severely ill 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_2 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).
In case of breast symptoms in men, it may be necessary to discontinue treatment to establish the underlying cause; however some cases have been resolved on continued therapy

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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

ATC Code: A02 BA02

Ranitidine is a specific, rapidly acting H_2-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 150mg dose effectively suppresses gastric acid secretion for twelve hours.

5.2 Pharmacokinetic properties

The bioavailability of ranitidine is consistently about 50%. Absorption of ranitidine after oral administration is rapid and peak plasma concentrations are usually achieved 2-3 hours after administration. Absorption is not significantly impaired by foods 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 balance studies with 150mg 3H-ranitidine 60-70% of an oral dose was excreted in urine and 26% in faeces. Analysis of urine excreted 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.

Special Patient 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.

5.3 Preclinical safety data

Extensive studies have been carried out in animals. The pharmacology of ranitidine hydrochloride shows it to be a surmountable H_2 receptor antagonist which produces an inhibition of gastric acid secretion. Extensive toxicological investigations have been conducted which predicted a very safe profile for clinical use. This safety has since been confirmed by extensive use in patients for many years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium hydrogen phosphate anhydrous
Sodium dihydrogen phosphate dihydrate
Saccharin sodium
Sorbitol solution 70%
Ethanol
Garden mint flavour
Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

16 months
1 month after first opening the bottle

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Bottle: Amber (Type III) glass.
Closure: HDPE, EPE wadded, tamper evident, child resistant closure.

Pack Size: 100ml and 300ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Perrigo Pharma International Designated Activity Company
The Sharp Building
Hogan Place
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22741/009/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th May 2007
Date of last renwal: 17th May 2012

10 DATE OF REVISION OF THE TEXT

November 2019