Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ranitidine 150mg/10ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10ml contains 150mg Ranitidine as ranitidine hydrochloride.

Excipients with known effect:
Sorbitol, liquid (non crystallising): 3000mg per 10ml
Sodium: 19.28mg per 10ml
Ethanol (96%):800mg per 10ml
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution

Clear pale yellow liquid with an odour of peppermint.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In adults Ranitidine 150mg/10ml Oral Solution is indicated for:

- the treatment of duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents.
- the prevention of NSAID associated duodenal ulcers.
- 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.
- 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.

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

The usual dosage is 150mg 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. 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 150mg twice daily may be given concomitantly with non-steroidal anti-inflammatory drug therapy.

In duodenal ulcer 300mg twice daily for 4 weeks results in healing rates which are higher than those at 4 weeks with ranitidine 150mg twice daily or 300mg 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.

Gastro-oesophageal reflux disease:

In the management of oesophageal reflux disease, the recommended course of treatment is either 150mg twice daily or 300mg 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 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. 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 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.

Chronic episodic dyspepsia:

For patients with chronic episodic dyspepsia the recommended course of treatment is 150mg 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 an oral dose of 150mg twice daily may be substituted for injections of ranitidine 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 can be given 2 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.

Children 12 years and over

For children 12 years and over the adult dosage is given.

Children (3 to 11 years)

See section 5.2 Pharmacokinetic Properties – Special Patient Populations.

Ranitidine 150mg/10ml Oral Solution contains approximately 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).

Patients over 50 years of age

See Section 5.2 Pharmacokinetic Properties (Special Patient Populations, Patients over 50 years of age)

Peptic Ulcer Acute Treatment:

The recommended oral dose for the treatment of peptic ulcer in children is 4mg/kg/day to 8mg/kg/day administered as two divided doses to a maximum of 300mg 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 in a maximum dose of 600mg (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.

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 150mg 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 twice daily should be instituted, followed, if need be, by maintenance treatment at 150mg 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 “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 150mg/10ml Oral Solution contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Ranitidine 150mg/10ml Oral Solution contains sodium. A dose of up to 150mg ranitidine contains less than 1mmol, essentially sodium free. A dose of 300mg ranitidine contains 39mg or 1.68mmol of sodium. Care should be taken with patients on a controlled sodium diet.

Ranitidine 150mg/10ml Oral Solution contains approximately 8% w/v ethanol (alcohol). Each 5ml of solution contains approximately 400mg of ethanol (96%), equivalent to 8ml of beer or 3ml of wine. High doses of Ranitidine Oral Solution, greater than 35ml (1,050mg ranitidine), contain more than 3g of alcohol. 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). Alternative formulations of ranitidine may be considered preferential in some populations. The amount of alcohol may modify or increase the effect of other medicines. The amount of alcohol in Ranitidine Oral Solution may impair the patient’s ability to drive or operate machinery (see section 4.7).

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, propanolol 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, gefitnib).

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 effects on labour, delivery or subsequent neonatal progress. Like other drugs ranitidine should only be used during pregnancy if considered essential.

Breast-feeding
Ranitidine is also excreted in human breast milk. Like other drugs ranitidine should only be used during nursing 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

Ranitidine 150mg/10ml Oral Solution has minor influence on the ability to drive and use machines due to very rare possibility of undesirable events dizziness and blurred vision (See Section 4.8).

The amount of alcohol in a large dose of Ranitidine 150mg/10ml Oral Solution may affect patient’s ability to drive or use machines.

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 (≥1/1,000, ≤1/100), rare (≥1/10,000, ≤1/1,000), very rare (≤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_2 receptor antagonists bradycardia and A-V Block.

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 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 Section, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; email: medsafety@hpra.ie.

4.9 Overdose

Symptoms and signs

Ranitidine Oral Liquid is very specific in action and no particular problems are expected following overdosage with

ranitidine.

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 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

Following oral administration of 150mg ranitidine, maximum plasma concentrations (300 to 550ng/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 300mg.

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 150mg 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 150mg 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 500mL/min, which exceeds glomerular filtration indicating net renal tubular secretion.

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 – 2.2h) 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

Sorbitol, liquid (non crystalising)
Ethanol (96%)
Disodium hydrogen phosphate dihydrate
Sodium dihydrogen phosphate dihydrate
Hydroxyethyl cellulose
Peppermint flavour
Saccharin sodium
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

Use within 3 months of opening.

6.4 Special precautions for storage

Do not store above 25°C.
Store in original carton/bottle in order to protect from light.

6.5 Nature and contents of container

Amber Ph Eur type 3 glass bottle containing 300ml with child resistant, tamper-evident, polypropylene lid.

6.6 Special precautions for disposal

No special requirements

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

7 MARKETING AUTHORISATION HOLDER

Focus Pharmaceuticals Ltd
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London EC4N 7BL
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8 MARKETING AUTHORISATION NUMBER

PA1338/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 19th June 2012

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