Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ranitistad 150 mg Film Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ranitidine 150 mg as ranitidine hydrochloride.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Round, white, biconvex, film coated tablets, engraved ‘150’ on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of conditions of the upper gastro-intestinal tract standing to benefit from reduction of gastric acid secretion including:
- Duodenal ulcer
- Benign gastric ulcer
- Reflux oesophagitis
- Zollinger-Ellison syndrome
- NSAID associated peptic ulcer
- Post-operative ulcer
- other conditions in which a reduction of gastric acid secretion is thought to be beneficial

Maintenance treatment of peptic ulcer.
Prophylaxis of NSAID associated duodenal ulcer.

4.2 Posology and method of adminstration

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

Duodenal, benign and postoperative gastric ulcers:
Two tablets (corresponding to 300mg ranitidine) after supper or at bedtime, or 1 tablet morning and night (corresponding to 300mg ranitidine daily). On this treatment ulcers generally heal within four weeks. In the occasional patient in whom the ulcer is not yet fully healed after four weeks’ treatment, the treatment should be continued for a further four weeks at the same dose.

In ulcers following non-steroidal anti-inflammatory drug (NSAID) therapy or associated with continued NSAIDs, eight to twelve weeks treatment may be necessary. For the prevention of NSAID associated duodenal ulcers ranitidine 150mg twice daily may be given concomitantly with NSAID therapy.

Maintenance treatment at a reduced dosage of 150 mg nocte may be used. Smoking is associated with a higher rate of ulcer relapse and such patients should be advised to stop smoking. In those who fail to comply with such advice a dose of 300 mg nocte provides additional therapeutic benefit in these patients over the 150 mg dosage regimen. Patients on

prolonged treatment (particularly those treated for more than one year) should be kept under regular surveillance.

For *reflux oesophagitis*, 2 tablets after supper or at bedtime, or 1 tablet morning and night, for up to 8 weeks (12 weeks if necessary).

In patients with moderate to severe oesophagitis, the dosage of ranitidine may be increased to 150 mg four times daily; alternatively 300 mg bd if necessary. The increased dose has not been associated with an increased incidence of unwanted effects.

Patients with very high gastric acid secretion, e.g. Zollinger-Ellison syndrome, should initially receive treatment with 1 tablet three times daily (= 450 mg ranitidine daily). If necessary, the dose may be increased to 600-900 mg ranitidine (4-6 tablets) daily.

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 150mg bd may be substituted for injectable preparations once oral feeding commences, in those patients considered to still be at risk from these conditions.

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

In obstetric patients, an oral dose of 150 mg may be given at commencement of labour followed by 150 mg at six-hourly intervals. It is recommended that in addition, a non-particulate antacid (e.g. sodium citrate) should be given prior to induction of anaesthesia in any patient requiring emergency general anaesthesia.

Patients may be stabilised on higher doses if measurement of gastric acid secretion demonstrates this to be necessary. (Daily doses up to 6g ranitidine have been given).

Doses may be given irrespective of mealtimes.

Dosage for children

Treatment with Ranitistad ®is generally not indicated for patients in this age -group. It should only be used if considered essential, and only for short-term treatment. The recommended oral dose for treatment of peptic ulcer in children is 2mg/kg to 4mg/kg twice daily to a maximum of 300 mg ranitidine per day.

Dosage guide for patients with renal impairment

Depending on the creatinine clearance (ml/min) or serum creatinine level (mg/100ml), the following dosages are recommended:

Creatinine clearance (ml/min)	Serum Creatinine (ca.)* (mg/100 ml)	Daily dose (oral) of Ranitistad ® 150/300
Up to 30	Over 2.6	150mg ranitidine
Over 30	Under 2.6	300mg ranitidine

- These serum creatinine levels are guidelines and do not indicate an identical degree of renal impairment in all patients. This is particularly true for older patients, in whom serum creatinine levels underestimate renal function. The following formula may be used to estimate creatinine clearance from measured serum creatinine (mg/100ml), age (years) and body weight (kg). For women, the results should be multiplied by a factor of 0.85.

- 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 and duration of administration

The film-coated tablets should be swallowed whole with sufficient amount of fluid.

Duration of administration (see posology)

4.3 Contraindications

Ranitistad ® must not be administered to patients with known hypersensitivity to the active ingredient, ranitidine hydrochloride, or to any of the other ingredients.

Isolated reports have indicated a relationship between the onset of acute intermittent porphyria and ingestion of ranitidine hydrochloride. Patients with a history of acute intermittent porphyria should therefore not be treated with Ranitistad ®.

4.4 Special warnings and special precautions for use

Special warnings
Ranitidine is not indicated for the treatment of minor gastro-intestinal complaints, such as a nervous stomach. The presence of a malignancy should be ruled out by suitable diagnostic procedures prior to the treatment of gastric ulcers in particular.

Regular supervision of patients who are taking NSAIDs concomitantly is recommended, especially in the elderly and in those with a history of peptic ulcer.

Before initiation of ranitidine treatment for any gastric ulceration, malignancy should be excluded by endoscopy and biopsy. Treatment may mask the symptoms of malignancy, delaying diagnosis.

Dosage reduction is required in patients with renal impairment (see 4.2 posology).

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

4.5 Interaction with other medicinal products and other forms of interaction

At higher doses of Ranitistad ® there may be a reduction in excretion of procainamide and N-acetylprocainamide due to inhibition of tubular secretion.

Note

As ranitidine absorption from the gastrointestinal tract may be reduced by the concurrent use of antacids or sucralfate, Ranitistad ® should be taken about 2 hours before such agents.

In clinical trials, ranitidine has not been shown to interfere with the biotransformation of theophylline and/or to produce elevated theophylline plasma concentration. However, there are isolated reports of the concomitant use of ranitidine and theophylline producing elevated theophylline plasma levels and signs and symptoms of theophylline overdosage.

Therefore, patients on concurrent treatment with Ranitistad ® should have their theophylline plasma concentrations monitored and the theophylline dosage adjusted as appropriate.

When concomitant treatment is being given with drugs whose absorption is pH-dependent, e.g. ketoconazole. The possibility of altered absorption of such drugs should be borne in mind.

The effects of alcohol may be potentiated by treatment with ranitidine hydrochloride.

4.6 Pregnancy and lactation

Ranitistad ® must not be administered during pregnancy and lactation unless considered essential by the physician, since little experience is yet available in humans, and none at all for the first trimester. Animal experiments have not shown any evidence of foetal damage.

The active ingredient is excreted in breast milk. Since nothing is known of the effects of ranitidine ingestion by neonates, and since impairment of gastric acid secretion cannot be excluded, breast-feeding should be avoided during ranitidine treatment.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The following symptoms may occasionally occur during treatment with ranitidine: headache, dizziness, skin rash, including rare cases suggestive of mild erythema multiforme, pruritis, diarrhoea, constipation, nausea. Most of these symptoms improved during continued treatment. There have been rare reports of arthralgia and myalgia. In very rare cases, increased hair loss (alopecia) has occurred during treatment with ranitidine.

Transient alterations in liver function tests have occurred; these were reversible on continued treatment or after ending treatment. Hepatitis with or without jaundice has rarely occurred during ranitidine treatment. These changes were usually reversible on stopping treatment.

Elevation of plasma creatinine has occurred rarely. The elevation was usually slight, and normalised during continued treatment with ranitidine.

Arrhythmias, e.g. tachycardia, bradycardia and A-V block, have occurred on very rare occasions.

Central nervous disorders, e.g. severe headache, confusion, anxiety, hallucinations, have rarely occurred during treatment with ranitidine. There have been isolated reports of depression during ranitidine treatment. Central nervous disorders were mostly seen in older or severely ill patients, and resolved on discontinuing treatment with ranitidine. In isolated reports of blurred vision (possibly due to impaired accommodation), the symptom was also reversible.

In isolated cases, gynaecomastia and disorders of sexual function (loss of libido, impaired potency) have occurred during treatment with ranitidine. A causal relationship between the use of ranitidine and these disorders has not so far been demonstrated.

Treatment with ranitidine has occasionally been associated with changes in the blood count (leucopenia and/or thrombocytopenia). These changes were usually reversible. There have been isolated reports of agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or aplasia.

Treatment with ranitidine has been associated in a few cases with acute hypersensitivity reactions (e.g. eosinophilia, urticaria, fever, hypotension, angioneurotic oedema, laryngeal spasm, bronchospasm, chest pain, acute pancreatitis, anaphylactic shock).

4.9 Overdose

6300mg ranitidine, equivalent to 42 Ranitistad ® 150 film coated tablets, equivalent to 21 Ranitistad ® 300 film coated tablets, has been taken orally daily for several months and tolerated with no side effects.

If an overdose of ranitidine is taken and symptoms of toxicity develop, gastric lavage should initially be carried out to remove unabsorbed active compound. If necessary, the patient may be connected to an artificial kidney (haemodialysis) to remove absorbed active compound from the blood.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 small 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 (150mg nocte) ranitidine produced mean reductions in gastric acid secretion of 42% and 69% respectively within 24 hours.

5.2 Pharmacokinetic properties

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.

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

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. 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.

Ranitidine is metabolised in the liver to Ranitidine-N-oxide, N-Desmethylranitidine, Ranitidine-S-oxide and the furane acid analogue. After oral administration, ranitidine is excreted via the kidneys; about 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.

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.

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

Ranitidine passes across the placental barrier. After i.v. injection as well as after oral administration of ranitidine during labour, the ranitidine concentrations found in the umbilical cord of a human infant corresponded to the serum concentrations of the mother. 12 hours after labour, the ranitidine concentrations in the infant were very low.

Ranitidine passes into the breast milk. 2 hours after intake, the mean ratio between milk and plasma concentration was 1.9 (area: 0.6 - 20.9).

Children

If not otherwise indicated, the pharmacokinetic data of children are essentially similar to those of adults.

Bioavailability

A bioavailability study performed in 1994 in 24 healthy volunteers revealed the following results as compared to the reference product:

	Test product	Reference product
C_{max}	1009.8 ± 331.3 ng/ml	1052.7 ± 359.8 ng/ml
T_{max}	3.00 ± 0.60 h	3.00 ± 1.05 h
AUC	4346.2 ± 1036.6 ng.h/ml	4514.2 ± 1148.8 ng.h/ml

5.3 Preclinical safety data

Acute toxicity

In the acute toxicity test, ranitidine showed a high therapeutic ratio. The LD_{50} after intravenous administration to mice and rats was 75-80 mg/kg, and after oral administration over 1000 mg/kg.

Chronic toxicity/subchronic toxicity

Parenteral administration

No evidence was found of any specific local irritation attributable to ranitidine. All treated mice, rats, rabbits and dogs remained clinically healthy. Rats received 13 or 20 mg/kg of ranitidine daily for five days, and rabbits 11.5 mg/kg daily for 5 days i.v., s.c. and i.m.

In another study model, rats and dogs received 2.5 or 5 mg/kg/day i.v. for 15 or 28 days. Some dogs occasionally showed soft faeces; no other changes attributable to ranitidine were observed.

Oral administration

Dogs treated with 50 or 100 mg/kg/day for 6 weeks occasionally passed soft faeces. In a study lasting 54 weeks, dogs received 25, 75 or 225-450 mg/kg/day. Passage of soft faeces, salivation and vomiting were occasionally observed. These symptoms were dose-dependent. Administration of 450 mg/kg/day occasionally gave rise to increased respiratory rate and muscle tremor. One dog died with clear signs of muscular incoordination. In a 78-week study on rats, 2000 mg/kg/day was well tolerated, though weight gain in these animals was less than in the control groups.

Mutagenic and oncogenic potential

In vitro and in vivo studies have shown no relevant evidence of a mutagenic potential of ranitidine.

Studies on mice and rats receiving lifelong treatment with ranitidine doses of up to 2000 mg/kg/day showed no evidence of an oncogenic potential of ranitidine. In this respect particular attention was paid to the gastric mucosa.

Reproductive toxicity

Embryotoxicity and fetotoxicity studies on rats and rabbits showed no evidence of teratogenic or other toxic effects on offspring. In rats, no adverse effects on fertility were seen either in the parental or the filial generation due to ranitidine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Croscarmellose sodium

Magnesium stearate
Colloidal anhydrous silica
Macrogol 3350
Hypromellose
Polydextrose
Titanium dioxide E171
Carnauba wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Polyamide/A1/PVC blister strips packed into boxes containing 20, 30, 50, 60 or 100 film coated tablets.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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Stadastraße 2 - 18
D-61118 Bad Vilbel
Germany

8 MARKETING AUTHORISATION NUMBER

PA 593/12/1

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