Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ranitidine Claris 25mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of Solution for Injection contains 25 mg Ranitidine

Each 2 ml ampoule contains 50 mg Ranitidine (as Ranitidine Hydrochloride)

Sodium and Potassium is present as less than 1 mmol per ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection or Infusion

A clear, colourless to pale yellow solution, free from visible particles.

pH between 6.70 and 7.30

Osmolarity of the drug product solution: 310.17 mOsmol/L

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults:
Ranitidine is indicated for the following conditions where a reduction of gastric acid secretion is desirable:
- Short term treatment of duodenal ulcer and benign gastric ulcer
- Short term treatment of reflux oesophagitis
- Zollinger-Ellison-Syndrome
- Prophylaxis of gastrointestinal haemorrhage from stress ulceration in seriously ill patients
- Prophylaxis of recurrent haemorrhage in patients with bleeding peptic ulcers
- Prophylaxis of acid aspiration (Mendelson's Syndrome) before general anaesthesia in patients considered to be at risk of acid aspiration.

Children (6 months 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

(See Section 5.2 Pharmacokinetic Properties – Special patient Populations)

Adults (including elderly)
Ranitidine Injection may be given either as a slow (over 2 minutes) intravenous injection up to a maximum of 50 mg, after dilution to a volume of 20 ml per 50 mg dose, which may be repeated every 6 to 8 hours, or as an intermittent intravenous infusion at a rate of 25 mg per hour for two hours; the infusion may be repeated at 6 to 8 hour intervals.

Peptic Ulcer Acute Treatment, Gastro-Oesophageal Reflux and Zollinger-Ellison-Syndrome

I.v. therapy for peptic ulcer disease and reflux oesophagitis, and Zollinger-Ellison-Syndrome is only indicated as long as oral therapy is not possible.

Prophylaxis of haemorrhage from stress ulceration or recurrent haemorrhage:

In the prophylaxis of upper gastro-intestinal haemorrhage from stress ulceration in seriously ill patients a priming dose of 50 mg as a slow intravenous injection followed by a continuous intravenous infusion of 0.125 - 0.250 mg/kg/hr may be preferred.
In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients or the prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration, parenteral administration may be continued until oral feeding commences. Patients considered to be still at risk may then be treated with Ranitidine tablets 150 mg twice daily.

Prophylaxis of stress ulceration in seriously ill patients.

The recommended dose for prophylaxis of stress ulceration is 1mg/kg (maximum 50 mg) every 6h to 8h.

Alternatively treatment can be continuous, administering 125 - 250 micrograms/kg/hr as continuous infusion.

Prophylaxis of Mendleson's syndrome:
In patients considered to be at risk of developing acid aspiration syndrome, Ranitidine Injection 50 mg may be given by slow intravenous injection 45 to 60 minutes before induction of general anaesthesia.

Children / Infants and Adolescents: (6 months to 18 years)
See section 5.2 Pharmacokinetic properties – Special Patient Populations.

Ranitidine injection may be given as a slow (over 2 minutes) i.v. injection up to a maximum of 50 mg every 6 to 8 hours.

Peptic Ulcer Acute Treatment, Gastro-Oesophageal Reflux
For acute treatment of peptic ulcer disease and gastro-oesophageal reflux in paediatric patients, Ranitidine injection may be administered at doses that have been shown to be effective for these diseases in adults and effective for acid suppression in critically ill children. The initial dose (2.0 mg/kg or 2.5 mg/kg, maximum 50 mg) may be administered as a slow intravenous infusion over 10 minutes, either with a syringe pump followed by a 3 mL flush with normal saline over 5 min, or following dilution with normal saline to 20 mL. Maintenance of pH > 4.0 can be achieved by intermittent infusion of 1.5 mg/kg every 6 h to 8 h. Alternatively treatment can be continuous, administering a loading dose of 0.45 mg/kg followed by a continuous infusion of 0.15 mg/kg/hr.

Neonates (under 1 month)
See Section 5.2 – Pharmacokinetic Properties – Special Patient Populations.

Renal Impairment:
Accumulation of ranitidine with resulting elevated plasma concentrations will occur in patients with severe renal impairment (creatinine clearance less than 50 ml/min). Accordingly, it is recommended in such patients that ranitidine be administered in doses of 25 mg.

Route of Administration
Intravenous injection

4.3 Contraindications

Ranitidine is contraindicated for patients known to have hypersensitivity to any component of the preparation.

4.4 Special warnings and precautions for use

Treatment with a histamine H2-antagonist may mask the symptoms associated with carcinoma of the stomach and may therefore delay diagnosis of the condition. Accordingly, where gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with Ranitidine is instituted.

Ranitidine is excreted via the kidney and so plasma levels of the drug are increased in patients with renal impairment. Accordingly, it is recommended in such patients that Ranitidine be administered in doses of 25 mg.

Bradycardia in association with rapid administration of Ranitidine Injection has been reported rarely, usually in patients with factors predisposing to cardiac rhythm disturbances. Recommended rates of administration should not be exceeded.

It has been reported that the use of higher than recommended doses of intravenous H2-antagonists has been associated with rises in liver enzymes when treatment has been extended beyond five days.

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.

This medicinal product contains less than 1 mmol (0.8745 mmol) sodium per 100 ml, i.e. essentially “sodium-free” and less than 1 mmol (0.718 mmol) potassium per 100ml, i.e. essentially “potassium free”.

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/plasma concentration (e.g. triazolam, midazolam, glipizide) or a decrease in absorption/plasma concentration (e.g. ketoconazole, itraconazole, posaconazole, atazanavir, delaviridine, gefitnib, erlotinib).

4) Interaction with cyanocobalamine :
Interaction to take into account due to the potential cyanocobalamine deficiency after prolonged treatment (many years) related the potential absorption decrease of vitamin B12 by means of a reduced acidity.

4.6 Fertility, pregnancy and lactation

Pregnancy
Data on a large number (> 1000) of exposed pregnancies indicate no adverse effects of ranitidine on pregnancy or the health of the fetus/newborn. To date, no other relevant epidemiological data are available.

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

Caution should be exercised when prescribing to pregnant woman.

Lactation
The active ingredient is excreted in breast milk. As nothing is known of the effect of ingestion of ranitidine in the infant and the possibility of disturbances of gastric acid secretion cannot be excluded, breast-feeding should be avoided during treatment.

Fertility
Ranitidine had no effect on male or female fertility in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

In the case of symptoms of hallucinations, dizziness, confusion or headache following the administration of Ranitidine, patients should not drive or use machinery until the symptoms have ceased.

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	(≥1/1,000 to <1/100)
Rare	(≥1/10,000 to <1/1,000)
Very rare	(<1/10,000)
Unknown	Cannot be estimated from the available data

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

Blood & Lymphatic System Disorders
Unknown: Blood count changes (leucopenia, thrombocytopenia). These are usually reversible. Agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or marrow aplasia.

Immune System Disorders
Uncommon: Hypersensitivity reactions (urticaria, angioneurotic oedema, fever, bronchospasm, hypotension and chest pain).
Unknown: Anaphylactic shock, Laryngeal spasm
These events have been reported after a single dose.

Psychiatric Disorders
Very Rare: depression
Unknown: Reversible mental confusion hallucinations, Agitation.
These have been reported predominantly in severely ill and elderly patients or suffering from renal impairment.

Nervous System Disorders
Common: Headache (sometimes severe) and dizziness
Very Rare: reversible involuntary movement disorders (tremors, myoclonus, and involuntary ocular movements).

Eye Disorders
Uncommon: Reversible blurred vision.
There have been reports of blurred vision, which is suggestive of a change in accommodation.

Cardiac Disorders
Unknown: As with other H2 receptor antagonists bradycardia and A-V Block with sinusal break and asystole.

Vascular Disorders
Unknown: Vasculitis.

Gastrointestinal Disorders
Common: Diarrhoea.
Unknown: Acute pancreatitis, nausea and constipation.

Hepatobiliary Disorders
Very Rare: Transient and reversible changes in liver function tests.
Unknown: Hepatitis (hepatocellular, hepatocanalicular or mixed) with or without jaundice, these were usually reversible.

Skin and Subcutaneous Tissue Disorders
Uncommon: Skin Rash.
Unknown: Erythema multiforme, alopecia, Pruritus.

Musculoskeletal and Connective Tissue Disorders
Unknown: Musculoskeletal symptoms such as arthralgia and myalgia.

Renal and Urinary Disorders
Unknown: Acute interstitial nephritis, Increased plasma creatinine.

Reproductive System and Breast Disorders
Unknown: Reversible impotence. Breast symptoms in men.

General disorders and administration site conditions
Asthenia

The safety of ranitidine has been assessed in children aged 0 to 16 years with acid-related disease and shows an adverse event profile resembling that in adults. There are limited long term safety data available, in particular regarding growth and development.

An increase in gastric pH in ventilated and seriously ill patients leads to increased bacterial counts in the GI tract and possibly in the bronchial system. An increased number of nosocomial pneumonia has also been reported.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Group: H2- receptor antagonist

ATC Code: A02BA02

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

The clinical data available mentions the use of ranitidine in children to prevent stress ulcers. No direct evidence for prevention of stress ulcers is available. Treatment for these patients is based on the observation that pH is above 4 after administration of ranitidine. The value of this surrogate parameter in children with stress ulcers remains to be established.

5.2 Pharmacokinetic properties

Absorption of ranitidine after intramuscular injection is rapid and peak plasma concentrations are usually achieved within 15 minutes of administration. Ranitidine is not extensively metabolised. The 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, 93% of an intravenous dose was excreted in urine and 5% in faeces. Analysis of urine excreted in the first 24 hours after dosing showed that 70% of the intravenous dose was eliminated unchanged. About 6% of the dose is excreted in the urine as the N-oxide, 2% as desmethyl ranitidine and 1-2% as the furoic acid analogue.

Special Patient Populations
Children/infants (6 months and above)
Limited pharmacokinetic data show that there were 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 intravenous ranitidine when correction is made for body weight. Pharmacokinetic data in infants is extremely limited but appears to be in line with that for older children.

Neonates (under 1 month)
Limited pharmacokinetic data from term babies undergoing treatment with Extracorporeal Membrane Oxygenation (EMCO) suggests that plasma clearance following iv administration may be reduced (1.5-8.2 ml/min/kg) and the half-life increased in the new-born. Clearance of ranitidine appeared to be related to the estimated glomerular filtration rate in the neonates.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

Ranitidine did not affect overall fertility in male and female rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride (for tonicity adjustment)

Potassium Dihydrogen Phosphate

Anhydrous Disodium Hydrogen Phosphate

Water for Injections.

Ranitidine Injection contains less than 1 mmol sodium (0.08475 per mL) and is essentially ‘sodium-free’.

6.2 Incompatibilities

See 6.6 Instructions for Use/Handling.
Please cross-refer to section 6.6 for stability following dilution.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

12 months

After first opening:
Single dose container. Use immediately after first opening.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated conditions.

6.4 Special precautions for storage

Do not store above 25ºC, store in original carton in order to protect from light.
Do not refrigerate or freeze.

Ranitidine Injection should not be autoclaved.

6.5 Nature and contents of container

2 ml colourless Type I glass ampoules.
Pack size: Each of these 2ml ampoules are placed in blisters and supplied in cartons of 5, 10 and 25 ampoules.

6.6 Special precautions for disposal and other handling

Ranitidine Injection has been shown to be compatible with the following intravenous infusion fluids in polyvinyl chloride bags and administrative set:-

0.9% Sodium Chloride BP
5% Dextrose BP
0.18% Sodium Chloride and 4% Dextrose BP
4.2% Sodium Bicarbonate BP
Hartmann's Solution.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 1389/11/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7 October 2011

10 DATE OF REVISION OF THE TEXT