SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

Ranitidine Injection USP – ACILOC INJECTION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Ranitidine Hydrochloride USP…….27.5 mg

Equivalent to Ranitidine……..…..….... 25 mg

Phenol USP…….…… 5%w/v

Water for Injection BP……..……..……...q.s.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Intravenous Injection / Intramuscular Injection

A clear, colorless to pale yellow solution, free from visible particles and fibres filled in 2.0 ml flint glass ampoules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:

Aciloc Injection is indicated for the treatment of duodenal ulcer, benign gastric ulcer, post - operative ulcer, reflux esophagitis, Zollinger - Ellison Syndrome and the following conditions where reduction of gastric secretion and acid output is desirable:

The prophylaxis of gastrointestinal 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, Aciloc tablets are also available.

Children (6 months to 18 years):

Aciloc Injection is indicated for the short term treatment of peptic ulcer and the treatment of gastro oesophageal reflux, including reflux oesophagitis and symptomatic relief of gastro oesophageal reflux disease.

4.2 Posology and method of administration

Adults (including elderly) / Adolescents (12 years and over)

Aciloc 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, or as an intramuscular injection of 50 mg (2 ml) every 6 to 8 hours.

Prophylaxis of haemorrhage from stress ulceration or recurrent haemorrhage:

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 Aciloc tablets 150 mg twice daily.
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.

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

Children / Infants (6 months to 11 years)
Aciloc 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 and Gastro-Oesophageal Reflux
Intravenous therapy in children with peptic ulcer disease is indicated only when oral therapy is not possible.

For acute treatment of peptic ulcer disease and gastro-oesophageal reflux in paediatric patients, Aciloc 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.

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.
Neonates (under 1 month)
Patients over 50 years of age

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

Route of Administration

Intravenous or intramuscular 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 H_2-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 Aciloc is instituted.

Aciloc 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 in Renal Impairment.

Bradycardia in association with rapid administration of Aciloc 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 H_2-\ 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 aciloc administration have been rare and inconclusive, aciloc should be avoided in patients with a history of this condition.

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). Postmarketing data indicate reversible mental confusion, depression, and hallucinations have been reported most frequently in severely ill and elderly patients.

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 secrection:
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 Nacetylprocainamide 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).

4) Erlotinib and medicinal products altering pH:
Concomitant administration of 300mg ranitidine and erlotinib decreased erlotinib exposure [AUC] and maximumconcentrations [Cmax] by 33% and 54%, respectively. However, when erlotinib was dosed in a staggered manner 2hours before or 10 hours after ranitidine 150mg b.i.d., erlotinib exposure [AUC] and maximum concentrations [Cmax] decreased only by 15% and 17%, respectively.

4.6 Pregnancy and lactation

Pregnancy

Aciloc 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.

Breast-feeding

Aciloc is also excreted in human breast milk. Like other drugs, Aciloc should only be used during pregnancy and 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

None known.

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 & 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 and elderly patient.	
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 asystole.
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).

There are limited long term safety data available, in particular regarding growth and development.

4.9 Overdose

Aciloc 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

Aciloc is a specific, rapidly acting histamine H_2-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
Absorption of aciloc after intramuscular injection is rapid and peak plasma concentrations are usually achieved within 15 minutes of administration.

Metabolism
Aciloc 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.

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.

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.

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

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

Phenol
Potassium Dihydrogen Phosphate
Disodium Hydrogen Phosphate Dihydrate
Water for Injection
Activated Charcoal

6.2 Incompatibilities

Not Applicable

6.3 Shelf-life

36 months

6.4 Special precautions for storage

Store below 30°C. Protect from light

6.5 Nature and contents of packing

2 ml colourless Type I glass ampoules, Pack size: 5 ampoules.

6.6 Instructions for use and handling

Aciloc Injection has been shown to be compatible with the following intravenous infusion fluids:-
0.9% Sodium Chloride BP
5% Dextrose BP
0.18% Sodium Chloride and 4% Dextrose BP
4.2% Sodium Bicarbonate BP
Hartmann's Solution.
All unused admixtures of Aciloc Injection with infusion fluids should be discarded 24 hours after preparation.
Although compatibility studies have only been undertaken in polyvinyl chloride infusion bags (in glass for Sodium Bicarbonate BP) and a polyvinyl chloride administration set it is considered that adequate stability would be conferred by the use of a polyethylene infusion bag.

7. MARKETING AUTHORISATION HOLDER

Cadila Pharmaceuticals Limited
Plot No. 1389, Trasad Road,
Dholka - 382 225, District: Ahmedabad, Gujarat, India.

8. MARKETING AUTHORISATION NUMBER(S)

07990/09979/NMR/2022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 Jan. 2023

10. DATE OF REVISION OF THE TEXT

July 2023