For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

RANITIN INJ 2 ml

1. Generic Name

Ranitidine Hydrochloride Injection I.P.

2. Qualitative and quantitative composition

Each ml contains:

Ranitidine Hydrochloride I.P

equivalent to Ranitidine .....25mg .

Water for Injection I.P…….q.s.

The excipients are charcoal (activated), dibasic sodium phosphate (anhydrous), potassium dihydrogen orthophosphate (anhydrous).

3. Dosage form and strength

Dosage form: Injection (Aqueous solution)

Strength: Ranitidine hydrochloride (25 mg)

4. Clinical particulars

4.1 Therapeutic indication

Ranitidine Hydrochloride Injection is indicated for the treatment of duodenal ulcer, benign gastric ulcer, post - operative ulcer, reflux oesophagitis, Zollinger - Ellison Syndrome.

4.2 Posology and method of administration

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

Ranitidine hydrochloride 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 Rantidine 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, Ranitidine hydrochloride 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)

Ranitidine hydrochloride 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, Ranitidine hydrochloride 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 5.3 – Pharmacokinetic properties – Other special populations)

Patients over 50 years of age

See section 5.3 – Pharmacokinetic properties – Other special populations)

Patients with renal impairment

Accumulation of ranitidine with resulting elevated plasma concentrations will occur in patients with 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.

Method of administration

Intravenous or intramuscular injection.

For instructions on dilution of the medicinal product before administration.

4.3 Contraindications

Ranitidine is contraindicated in patients with a known hypersensitivity to ranitidine or any of the excipients.

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 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 in patients with renal impairment.

Bradycardia in association with rapid administration of Ranitidine Hydrochloride 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.

Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks. Ranitidine should therefore be avoided in patients with a history of acute porphyria.

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 reported, 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, reported most frequently in severely ill and elderly patients

4.5 Drugs 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 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 (e.g. triazolam, midazolam, glipizide) or a decrease in absorption (e.g. ketoconazole, atazanavir, delaviridine, gefitnib).

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 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

<u>Pregnancy</u>

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. Like other drugs, ranitidine should only be used during pregnancy if considered essential.

Breast-feeding

Rantidine is also excreted in human breast milk. Like other drugs, ranitidine should only be used during breast-feeding 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 reported

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 patients, in elderly and nephropathic 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 H2 receptor antagonists bradycardia, A-V block, asystole,

cardiac arrest 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).

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 side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting

4.9 Overdose

Symptoms and signs

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

Treatment

Symptomatic and supportive therapy should be given as appropriate.

5. Pharmacological properties

5.1 Mechanism of Action

Pharmacotherapeutic group: H2-receptor antagonists

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.

5.2 Pharmacodynamic properties

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.

5.3 Pharmacokinetic properties

Absorption

Absorption of ranitidine after intramuscular injection is rapid and peak plasma concentrations are usually achieved within 15 minutes of administration.

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 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.

Other special 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)

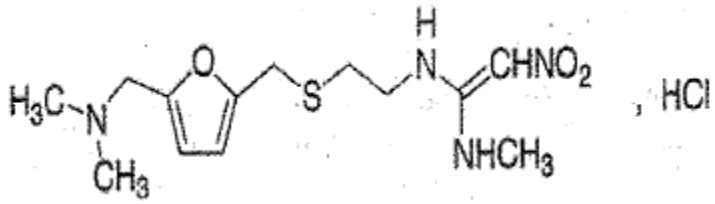
Limited pharmacokinetic data from term babies undergoing treatment with Extracorporeal Membrane Oxygenation (EMCO) suggests that plasma clearance following iv administration may be reduced (1.5-8.2 ml/min/kg) and the half-life increased in the new-born. Clearance of ranitidine appeared to be related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

6. Nonclinical properties

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.

7. Description

Ranitidine Hydrochloride is N-2-[[[5-(dimethylamino}methyl] furan-2-yl]methyl]thio]ethyl]-N-methyl-2-nitroethene-1,1-diamine hydrochloride. The empirical formula is C13H22N4O3S●HCl, representing a molecular weight of 350.87.



Ranitidine is a white to pale yellow, crystalline powder.

Product Description:

Ranitidine injection is a clear, colourless to pale yellow liquid.

8. Pharmaceutical particulars

8.1 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned below:

- 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 Ranitidine hydrochloride 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.

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

Available in 2 ml ampoules.

8.4 Storage and handing instructions

Store below 30°C.

Do not freeze.

Protect from light.

9. Patient Counselling Information

RANITIN INJ 2 ml

Ranitidine Hydrochloride Injection I.P.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

1. What RANITIN INJ is and what they are used for
2. What you need to know before you use RANITIN INJ
3. How to use RANITIN INJ
4. Possible side effects
5. How to store RANITIN INJ
6. Contents of the pack and other information

9.1 What RANITIN INJ is and what it is used for

RANITIN contains a medicine called ranitidine. This belongs to a group of medicines called H_2-receptor antagonists. It lowers the amount of acid in your stomach.

For adults (including the elderly) RANITIN is used to:

- heal and stop ulcers in the stomach, or the part of the gut it empties into (the duodenum)
- stop ulcers from bleeding.
- improve problems caused by acid in the food pipe (oesophagus) or too much acid in the

stomach. Both of these can cause pain or discomfort sometimes known as ‘indigestion’, ‘dyspepsia’ or ‘heartburn’.

- stop acid coming up from the stomach while under anaesthetic during an operation.

For children (6 months to 18 years) RANITIN is used to:

- heal ulcers in the stomach, or the part of the gut it empties into (the duodenum)
- heal and stop problems caused by acid in the food pipe (oesophagus) or too much acid in the stomach. Both of these can cause pain or discomfort sometimes known as “indigestion”, “dyspepsia” or “heartburn”.

9.2 What you need to know before you use RANITIN INJ.

Do not have RANITIN INJ if:

- You are allergic to ranitidine or any of the other ingredients of this medicine.
- If you are not sure, talk to your doctor or pharmacist before having RANITIN INJ.

Warnings and precautions

Check with your doctor or pharmacist before having your medicine if:

- you have stomach cancer.
- you have kidney problems. You will need to have a different amount of RANITIN INJ.
- you have had stomach ulcers before.
- you have a history of heart trouble.
- you have a rare condition called acute porphyria.
- you are over 65 years old.
- you have lung disease.
- you are diabetic.
- you have any problems with your immune system.
- If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before having this medicine**.**

Other medicines and RANITIN INJ

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines that you buy without a prescription and herbal medicines. This is because RANITIN INJ can affect the way some other medicines work. Also some other medicines can affect the way RANITIN INJ works.

In particular tell your doctor or pharmacist if you are taking any of the following medicines:

- lidocaine, a local anaesthetic
- propranolol, procainamide or n-acetylprocainamide, for heart problems
- diazepam, for worry or anxiety problems
- phenytoin, for epilepsy
- theophylline, for breathing problems (asthma)

- warfarin, for thinning your blood
- glipizide, for lowering blood glucose
- atazanavir or delavirdine, for treating HIV infection
- triazolam, for insomnia
- gefitinib, for lung cancer
- ketoconazole, an anti-fungal medicine, sometimes used for treating thrush.
- erlotinib; for certain types of cancer

Midazolam is a medicine that may be given to you just before you have an operation. Tell the doctor you are taking RANITIN INJ before your operation in case he or she wants to give you midazolam.

If you are taking erlotinib, a drug used for the treatment of certain types of cancer, talk to your doctor before you take RANITIN INJ. Ranitidine contained in RANITIN INJ may decrease the amount of erlotinib in your blood and your doctor may need to adjust your treatment if it is used while you are receiving erlotinib.

If you are not sure if any of the above apply to you, talk to your doctor, pharmacist or nurse before having RANITIN INJ.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before having this medicine. You should not take this medicine unless your doctor advises it is essential.

RANITIN INJ contains sodium.

RANITIN INJ contains less than 23 mg of sodium and is therefore essentially sodium-free.

RANITIN INJ contains less than 39 mg (1mmol) of potassium and is therefore essentially potassium-free.

9.3 How to use RANITIN INJ

You will never be expected to give yourself this medicine. It will always be given to you by a person who is trained to do so.

Having this medicine

RANITIN INJ will be given to you either:

- as a single injection into a muscle
- as a slow infusion into a vein. This is where the drug is slowly given to you over a few minutes
- as a continuous infusion into a vein. This is where the drug is slowly given to you over a few hours.

The usual dose for an adult (including the elderly) and adolescents (12 years and older) is 50 mg every 6 to 8 hours, as a single injection into a muscle.

Different doses may also be given to you as a slow infusion or continuous infusion, depending on what condition you are being treated for.

Use in children and infants (6 months to 11 years)

Your doctor will give RANITIN INJ by a slow injection into a vein. The maximum dose is 50 mg every 6 or 8 hours. It is usually only given while your child is unable to take RANITIN INJ by mouth.

If you are given more RANITIN INJ than you should

Your doctor or nurse will give you RANITIN INJ so it is unlikely that you will receive too much. If you think you have been given too much or have missed a dose, tell your doctor or nurse.

9.4 Possible Side Effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects may happen with this medicine.

Stop taking RANITIN INJ and see a doctor straight away, if you notice any of the following serious side effects, you may need urgent medical treatment:

- allergic reactions, the signs may include:

- rash, itching or hives on the skin.

- swelling of your face, lips, tongue or other parts of the body.

- chest pain, shortness of breath, wheezing or having trouble breathing.

- unexplained fever and feeling faint, especially when standing up.

- kidney problems, which can lead to back pain, fever, pain when passing urine, blood in the urine and changes in blood tests.

- severe stomach pain, this may be a sign of something called 'pancreatitis'
- a slow or irregular heartbeat

Check with your doctor **at your next visit** if you notice any of the following:

Uncommon (may affect up to 1 in 100 people)

- stomach pain
- constipation
- feeling sick (nausea)

Rare (may affect up to 1 in 1,000 people)

- skin rash

Rare side effects that may show up in blood tests:

- increase of serum creatinine in the blood (kidney function test)
- changes to liver function

Check with your doctor **as soon as possible** if you notice any of the following:

Very rare (may affect up to 1 in 10,000 people)

- there can be changes in the level of certain substances in your blood. This can lead to you feeling unusually tired or short of breath and being more likely to bruise or get an infection

- feeling depressed, confused, seeing or hearing unexplained things (hallucinations)
- headache (sometimes severe)
- feeling dizzy or having blurred vision
- your joints or muscles are painful or swollen or you cannot control their movement
- your small blood vessels can become swollen (known as 'vasculitis'). Signs of this can include: a rash, swollen joints or kidney problems
- your liver can become swollen. This can lead to: nausea (feeling sick) or vomiting (being sick), loss of appetite or generally feeling unwell, itching, fever, yellowing of the skin and eyes or dark coloured urine.
- flushing or marks on your skin that look like targets
- unexplained hair loss
- diarrhoea
- impotence
- breast tenderness and/or breast enlargement
- breast discharge
- awareness of the heart beat and/or increased heart rate

Not known (frequency cannot be estimated from the available data)

- shortness of breath

❖ **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store RANITIN INJ

Keep this medicine out of the sight and reach of children.

- Do not use this medicine after the expiry date, which is stated on the label. The expiry date refers to the last day of that month.
- Store below 30°C
- Protect from light
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

9.6 Contents of the pack and other information

What RANITIN INJ contains

- The active substance is ranitidine (as the hydrochloride) 25 mg.

- The other ingredients are charcoal (activated), dibasic sodium phosphate (anhydrous), potassium dihydrogen orthophosphate (anhydrous).

What RANITIN INJ looks like and contents of the pack

- RANITIN INJ is a clear, colourless to pale yellow liquid. You shouldn't be able to see any particles in it.
- Cartons contain 2 ml glass ampoules.

10. Details of manufacturer

Manufactured by:

Torrent Pharmaceutical Ltd.

Indrad-382 721, Dist, Mehsana, INDIA

At: 2,3, 4 & 5, Sec. 6-B, IIE, SIDCUL, Ranipur, Haridwar-249 403

11. Details of permission or licence number with date

5/UA/LL/SC/P-2018 issued on 09.10.2020

12. Date of revision

FEB-2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/RANITIN INJ 25 mg/FEB-2022/03/PI