SMPC

KADINE INJECTION
Cimetidine Injection 200mg/2ml

Module 1 :

ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

SMPC: KADINE INJECTION Cimetidine Injection 200mg/2ml

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

KADINE Cimetidine Injection 200mg/2ml

2. Qualitative and quantitative composition

Each 2ml contains: Cimetidine hydrochloride equivalent to 200 mg Cimetidine.

3. Pharmaceutical form

Injection

Clear, colourless sterile solution.

4. Clinical particulars

4.1 Therapeutic indications

(1) Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks and there is rarely reason to use cimetidine at full dosage for longer than 6 to 8 weeks. Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of oral cimetidine and antacids is not recommended, since antacids have been reported to interfere with the absorption of oral cimetidine.

(2) Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of active ulcer. Patients have been maintained on continued treatment with cimetidine 400 mg h.s. for periods of up to five years.

(3) Short-term treatment of active benign gastric ulcer. There is no information concerning usefulness of treatment periods of longer than 8 weeks.

(4) Prevention of upper gastrointestinal bleeding in critically ill patients.

(5) The treatment of pathological hypersecretory conditions (i.e., Zollinger-Ellison Syndrome, systemic mastocytosis, multiple endocrine adenomas).

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4.2 Posology and method of administration

Parenteral Administration

Where required parenteral administration may be used.

The dose with intravenous or intramuscular injections, is normally 200 mg. Injections may be repeated at 4 or 6 hourly intervals.

The 200 mg injection for intravenous use should be diluted in 0,9% Normal Saline (or other compatible solution) to a total volume of 20 mL and given very slowly, at least over 2 minutes.

The dose by intravenous infusion is usually 50 to 100 mg/hour for 2 hours and repeated at 4 to 6 hourly intervals. The maximum infusion rate should not usually exceed 150 mg/hour or 2 mg/kg body mass/hour. Intravenous infusion is preferred in patients where cardiovascular impairment is present.

Cimetidine injection has been shown to be compatible with Dextrose (5 and 10 %), and Normal Saline (0,9 %) solutions for intravenous infusion and the resultant solution is stable for 1 week at normal room temperature. Patients with creatinine clearance less than 30 cc/min. who are being treated for prevention of upper gastrointestinal bleeding should receive half the recommended dose.

Do not administer product unless solution is clear and container is undamaged. Discard unused portion. All parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

4.3 Contraindications

Cimetidine is contraindicated for patients known to have hypersensitivity to the product.

Cimetidine is not recommended for minor digestive complaints. It is also not recommended for patients with impaired renal function.

4.4 Special warnings and precautions for use

General: Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of cimetidine hydrochloride injection by intravenous bolus.

Symptomatic response to cimetidine therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states (see ADVERSE REACTIONS) have been observed on occasion,

predominantly, but not exclusively, in severely ill patients. Advancing age (50 or more years) and pre-existing liver and/or renal disease appear to be contributing factors. In some patients these confusional states have been mild and have not required discontinuation of cimetidine therapy. In cases where discontinuation was judged necessary, the condition usually cleared within 3 to 4 days of drug withdrawal.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month toxicity study conducted in rats, at dose levels of 150, 378 and 950 mg/kg/day (approximately 8 to 48 times the recommended human dose), there was a small increase in the incidence of benign Leydig cell tumors in each dose group; when the combined drug-treated groups and control groups were compared, this increase reached statistical significance. In a subsequent 24 month study, there were no differences between the rats receiving 150 mg/kg/day and the untreated controls. However, a statistically significant increase in benign Leydig cell tumor incidence was seen in the rats that received 378 and 950 mg/kg/day. These tumors were common in control groups as well as treated groups and the difference became apparent only in aged rats.

Cimetidine has demonstrated a weak antiandrogenic effect. In animal studies this was manifested as reduced prostate and seminal vesicle weights. However, there was no impairment of mating performance or fertility, nor any harm to the fetus in these animals at doses 8 to 48 times the full therapeutic dose of cimetidine, as compared with controls. The cases of gynecomastia seen in patients treated for one month or longer may be related to this effect.

In human studies, cimetidine has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity.

Pediatric Use: Clinical experience in pediatric patients is limited. Therefore, cimetidine therapy cannot be recommended for pediatric patients under 16, unless, in the judgment of the physician, anticipated benefits outweigh the potential risks. In very limited experience, doses of 20 to 40 mg/kg per day have been used.

Immunocompromised Patients: In immunocompromised patients, decreased gastric acidity, including that produced by acid-suppressing agents such as cimetidine, may increase the

possibility of a hyperinfection of strongyloidiasis.

4.5 Interaction with other medicinal products and other forms of interaction

Cimetidine, apparently through an effect on certain microsomal enzyme systems, has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, nifedipine, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole, thereby delaying elimination and increasing blood levels of these drugs.

Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when cimetidine is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either cimetidine 300 mg q.i.d. or 800 mg h.s. concomitantly with a 300 mg b.i.d. dosage of theophylline extended-release tablets demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

Dosage of the drugs mentioned above and other similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered cimetidine to maintain optimum therapeutic blood levels.

Alteration of pH may affect absorption of certain drugs (e.g., ketoconazole). If these products are needed, they should be given at least 2 hours before cimetidine administration.

Additional clinical experience may reveal other drugs affected by the concomitant administration of cimetidine.

4.6 Pregnancy and lactation

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Pregnancy:

Pregnancy Category B: Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cimetidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Cimetidine is secreted in human milk and, as a general rule, nursing should not be undertaken while a patient is on a drug.

4.7 Effects on ability to drive and use machines

No date provided.

4.8 Undesirable effects

Adverse effects reported in patients taking cimetidine are described below by body system. Incidence figures of 1 in 100 and greater are generally derived from controlled clinical studies.

Gastrointestinal: Diarrhea (usually mild) has been reported in approximately 1 in 100 patients.

CNS: Headaches, ranging from mild to severe, have been reported in 3.5% of 924 patients taking 1600 mg/day, 2.1% of 2,225 patients taking 800 mg/day and 2.3% of 1,897 patients taking placebo. Dizziness and somnolence (usually mild) have been reported in approximately 1 in 100 patients on either 1600 mg/day or 800 mg/day.

Reversible confusional states, e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation, have been reported predominantly, but not exclusively, in severely ill patients. They have usually developed within 2 to 3 days of initiation of cimetidine therapy and have cleared within 3 to 4 days of discontinuation of the drug.

Endocrine: Gynecomastia has been reported in patients treated for one month or longer. In patients being treated for pathological hypersecretory states, this occurred in about 4% of cases while in all others the incidence was 0.3% to 1% in various studies. No evidence of induced endocrine dysfunction was found, and the condition remained unchanged or returned toward normal with continuing cimetidine treatment.

Reversible impotence has been reported in patients with pathological hypersecretory disorders,

e.g., Zollinger-Ellison Syndrome, receiving cimetidine, particularly in high doses, for at least 12 months (range 12 to 79 months, mean 38 months). However, in large-scale surveillance studies at regular dosage, the incidence has not exceeded that commonly reported in the general population.

Hematologic: Decreased white blood cell counts in cimetidine-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of pancytopenia or aplastic anemia have also been reported. As with some other H2-receptor antagonists, there have been extremely rare reports of immune hemolytic anemia.

Hepatobiliary: Dose-related increases in serum transaminase have been reported. In most cases they did not progress with continued therapy and returned to normal at the end of therapy. There have been rare reports of cholestatic or mixed cholestatic hepatocellular effects. These were usually reversible. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. However, as in the occasional liver injury with other H2-receptor antagonists, in exceedingly rare circumstances fatal outcomes have been reported.

There has been reported a single case of biopsy-proven periportal hepatic fibrosis in a patient receiving cimetidine.

Rare cases of pancreatitis, which cleared on withdrawal of the drug, have been reported.

Hypersensitivity: Rare cases of fever and allergic reactions including anaphylaxis and hypersensitivity vasculitis, which cleared on withdrawal of the drug, have been reported.

Renal: Small, possibly dose-related increases in plasma creatinine, presumably due to competition for renal tubular secretion, are not uncommon and do not signify deteriorating renal function. Rare cases of interstitial nephritis and urinary retention, which cleared on withdrawal of the drug, have been reported.

Cardiovascular: Rare cases of bradycardia, tachycardia and A-V heart block have been

reported with H2-receptor antagonists.

Musculoskeletal: There have been rare reports of reversible arthralgia and myalgia; exacerbation of joint symptoms in patients with pre-existing arthritis has also been reported. Such symptoms have usually been alleviated by a reduction in cimetidine dosage. Rare cases of polymyositis have been reported, but no causal relationship has been established.

Integumental: Mild rash and, very rarely, cases of severe generalized skin reactions including Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma have been reported with H2-receptor antagonists. Reversible alopecia has been reported very rarely.

Immune Function: There have been extremely rare reports of strongyloidiasis hyperinfection in immunocompromised patients.

4.9 Overdose

Studies in animals indicate that toxic doses are associated with respiratory failure and tachycardia which may be controlled by assisted respiration and the administration of a beta blocker.

Reported acute ingestions orally of up to 20 grams have been associated with transient adverse effects similar to those encountered in normal clinical experience. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy, should be employed.

There have been reports of severe CNS symptoms, including unresponsiveness, following ingestion of between 20 and 40 grams of cimetidine, and extremely rare reports following concomitant use of multiple CNS- active medications and ingestion of cimetidine at doses less than 20 grams. An elderly, terminally ill dehydrated patient with organic brain syndrome receiving concomitant antipsychotic agents and cimetidine 4800 mg intravenously over a 24 hour period experienced mental deterioration with reversal on cimetidine discontinuation.

There have been two deaths in adults who were reported to have ingested over 40 grams orally on a single occasion.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Cimetidine competitively inhibits the action of histamine at the histamine H2 receptors of the parietal cells and thus is a histamine H2-receptor antagonist.

Cimetidine is not an anticholinergic agent. Studies have shown that cimetidine inhibits both daytime and nocturnal basal gastric acid secretion. Cimetidine also inhibits gastric acid secretion stimulated by food, histamine, pentagastrin, caffeine and insulin.

5.2 Pharmacokinetic properties

The half-life of cimetidine is approximately 2 hours. Both oral and parenteral (I.V. or I.M.) administration provide comparable periods of therapeutically effective blood levels; blood concentrations remain above that required to provide 80% inhibition of basal gastric acid secretion for 4 to 5 hours following a dose of 300 mg.

Steady-state blood concentrations of cimetidine with continuous infusion of cimetidine hydrochloride are determined by the infusion rate and clearance of the drug in the individual patient. In a study of peptic ulcer patients with normal renal function, an infusion rate of 37.5 mg/hour produced average steady-state plasma cimetidine concentrations of about 0.9 mcg/mL. Blood levels with other infusion rates will vary in direct proportion to the infusion rate.

The principal route of excretion of cimetidine is the urine. Following parenteral administration, most of the drug is excreted as the parent compound; following oral administration, the drug is more extensively metabolized, the sulfoxide being the major metabolite. Following a single oral dose, 48% of the drug is recovered from the urine after 24 hours as the parent compound. Following I.V. or I.M. administration, approximately 75% of the drug is recovered from the urine after 24 hours as the parent compound.

5.3 Preclinical safety data

No further relevant information other than that which is included in other sections of the

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Summary of Product Characteristics

6. Pharmaceutical particulars

6.1 List of excipients

Hydrochloric acid B.P.

Water for Injections B.P

6.2 Incompatibilities

No data provided.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze. Store in the original package in ord er to protect from light.

6.5 Nature and contents of container

Type I clear colorless glass ampoule of 2ml capacity. Each pack contains 1, 5, 10, 50, 100 ampoules*.

*Not all pack sizes may be marketed

6.6 Special precautions for disposal

Use as directed by the physician.
Keep out of reach of children.
If only part used, discard the remaining solution.
Discard the ampoule if the contents are discoloured.

7. Marketing authorisation holder

NASAJONES INDUSTRIES LIMITED
No 31/32 Office Complex Middle Road by Ado Bayero Square S/G, Kano.

Manufactured By:
GUIZHOU TIANDI PHARMACEUTICAL CO., LTD
No 6 Baokang Road Hongxing Pharmaceutical Industrial Park, Xingyl, Guizhou, China

10 Ampoules

KADINE

CIMETIDINE INJECTION

200mg/2ml

I.M./I.V.

NAFDAC Reg. No.:

For
I.M./IV.

KADINE
CIMETIDINE INJECTION

COMPOSITION:
Chaque 2ml ampoule contient cimetidine 200mg.
/Each 2ml ampoule contains cimetidine 200mg.

POSOLOGIE/DOSAGE:
Selon les directives du médecin. Voir la notice à l'interieur.
/As prescribed by the physician. See leaflet inside.
CONSERVATION/STORAGE:
Conserver en dessous de 30°C. A l'abri de la lumière et de l'humidité
/Store below 30°C. Protect from light and moisture.

KADINE
CIMETIDINE INJECTABLE

10 Ampoules

KADINE

CIMETIDINE INJECTABLE

200mg/2ml

I.M./I.V.

NAFDAC Reg. No.:

Pour
I.M./IV.

Batch No.:
Mfg.\Fab Date:
Exp./Per Date:

MANUFACTURED FOR:
Nasajones Industries Limited
No 31/32 Office Complex Middle Rooad by Ado Bayero Square S/G,Kano.

Manufactured By:
Guizhou Tiandi Pharmaceutical Co.,Ltd.
No.6 Baokang road, hongxing pharmaceutical industrial park, xingyi, Guizhou, China.