1.3.1 Summary of Product Characteristics (SmPC)

Cimetidine 200mg/2ml injection

1. Name of the medicinal product

Cimetidine 200mg/2ml injection

2. Qualitative and quantitative composition

Each ampoule contains 200 mg Cimetidine per 2 mL.

3. Pharmaceutical form

Injection for intravenous or intramuscular injections.

4. Clinical particulars

4.1 Therapeutic indications

The treatment of benign gastric and duodenal ulcers, reflux oesophagitis, Zollinger-Ellison syndrome and in other conditions associated with gastric hypersectetory states, such as systemic mastocytosis and multiple endocrine adenomas. It is also indicated at reduced dosage for duodenal ulcer recurrence in selected patients.

4.2 PHARMACOLOGICAL ACTION:

Cimetidine is a histamine H2-receptor antagonist. Its main action is to inhibit gastric acid secretion. It also inhibits competitively the other actions of histamine mediated by H2-receptors. The decrease in gastric acid secretion occurs regardless of the nature of the physiological stimulus to secretion, i.e. basal or unstimulated secretion, is reduced. Both the volume of secretion and the concentration of acid in the secretion are reduced.

4.3 Posology and method of administration

DOSAGE AND DIRECTIONS FOR USE:

Cimetidine therapy cannot be recommended for children.

The total daily use by any route should not exceed 2.4 g

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.

4.4 CONTRA-INDICATIONS:

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

4.5 PRECAUTIONS

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.

4.6 SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Adverse reactions to cimetidine are generally infrequent and are usually reversible following a reduction of dosage or withdrawal of therapy. The commonest side-effects reported have been diarrhea, dizziness, tiredness, headache, and rashes. Reversible confusional states, especially in the elderly or in seriously ill patients such as those with renal failure, have occasionally occurred. Cimetidine has a weak anti-androgenic effect and gynaecomastia and impotence have also occasionally occurred in men receiving relatively high doses for conditions such as the Zollinger-Ellison syndrome.

Before giving cimetidine to patients with gastric ulcers the possibility of malignancy should be excluded since cimetidine may mask symptoms and delay diagnosis. It should be given in reduced dosage to patients with impaired renal function. For further details of administration in renal failure, intravenous injections of cimetidine should be given slowly and intravenous infusion is recommended in patients with cardiovascular impairment.

4.7 INTERACTIONS

Cimetidine has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam and theophylin, thereby delaying elimination and increasing blood levels of these medicines.

Dosages of the medicines mentioned above and other similarly metabolized medicines may require adjustment when starting or stopping concomitantly administered Cimetidine to maintain safe, optimum therapeutic blood levels.

4.8 OVERDOSAGE

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

Pharmacotherapeutic Group: H2-receptor Antagonists, ATC code: A02BA01
Cimetidine is a histamine H2-receptor antagonist which rapidly inhibits both basal and stimulated gastric secretion of acid and reduces pepsin output. It is a reversible, competitive antagonist, and is used as an anti-ulcer drug. It is highly selective in its action, is virtually without effect on H1 receptors, or indeed on receptors for other autocoids or drugs. Despite the widespread distribution of H2-receptors in the body, Cimetidine interferes remarkably little with physiological functions other than gastric secretion, implying that the extragastric H2-receptors are of minor physiological importance.
However, H2 blockers like Cimetidine do inhibit those effects on the cardiovascular and other systems that are elicited through the corresponding receptors by exogenous or endogenous histamine.
Cimetidine inhibits gastric acid secretion elicited by histamine or other H2 agonists in a dose-dependent, competitive manner; the degree of inhibition parallels the plasma concentration of the drug over a wide range. In addition, the H2 blockers inhibit gastric secretion elicited by muscarinic agonists or by gastrin, although this effect is not always complete.

This breadth of inhibitory effect is not due to non-specific actions at the receptors for these other secretagogues. Rather, this effect, which is non-competitive and indirect, appears to indicate either that these two classes of secretagogues utilise histamine as the final common mediator or, more probably, that ongoing histaminergic stimulation of the parietal cell is important for amplification of the stimuli provided by ACh or gastrin when they act on their own discrete receptors. Receptors for all three secretagogues are present on the parietal cell. The ability of H2 blockers to suppress

responses to all three physiological secretagogues makes them potent inhibitors of all phases of gastric acid secretion. Thus these drugs will inhibit basal (fasting) secretion and nocturnal secretion and also that stimulated by food, sham feeding, fundic distension, insulin, or caffeine. The H2 blockers reduce both the volume of gastric juice secreted and its hydrogen ion concentration. Output of pepsin, which is secreted by the chief cells of the gastric glands (mainly under cholinergic control), generally falls in parallel with the reduction in volume of the gastric juice. Secretion of intrinsic factor is also reduced, but it is normally secreted in great excess, and absorption of vitamin B12 is usually adequate even during long-term therapy with H2 blockers.
Concentrations of gastrin in plasma are not significantly altered under fasting conditions; however, the normal prandial elevation of gastrin concentration may be augmented, apparently as a consequence of a reduction in the negative feedback that is normally provided by acid.

5.2 Pharmacokinetic properties
Cimetidine is rapidly and virtually completely absorbed from the gastro-intestinal tract. Absorption is little impaired by food or by antacids. Peak plasma concentrations are obtained about an hour after administration on an empty stomach, and about 2 hours after administration with food. The duration of action is reported to be prolonged by administration with food. Peak concentrations in plasma are attained in about 1 to 2 hours. Hepatic first-pass metabolism results in bioavailabilities of about 60% for Cimetidine. The elimination half-life is about 2-3 hours. Cimetidine is eliminated primarily by the kidneys, and 60% or more may appear in the urine unchanged; much of the rest is oxidation products. Small amounts are recovered in the stools.
Cimetidine crosses the placental barrier and is excreted in milk. It does not readily cross the blood-brain barrier.

6. Pharmaceutical particulars
6.1 List of excipients
None

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store in a cool place below 30°C. Protect from light.
KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container
Ampoule.

6.6 Special precautions for disposal and other handling
Nothing stated.

7. Marketing authorisation holder
Jiangsu Ruinian Qianjin Pharmaceutical Co., Ltd.
Chuanbu Village, Dingshu town, Yixing city, Jiangsu province, China.