PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

PHARMA-Q CIMETIDINE INJECTION 200 mg/2 ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 ml contains 200 mg cimetidine as hydrochloride.

For full list of excipients, see section 6.1

Sugar free.

3 PHARMACEUTICAL FORM

Solution for injection.

A clear, colourless solution in 2 ml clear colourless ampoules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PHARMA-Q CIMETIDINE INJECTION is indicated in the treatment of:

- Gastric and duodenal ulcers.
- Oesophageal reflux.
- Zollinger-Ellison syndrome.
- Other conditions associated with gastric hypersecretory states.

PHARMA-Q CIMETIDINE INJECTION is also indicated in the management of:

- Those patients who are at high risk from haemorrhage of the upper gastro-intestinal tract due to hepatic failure.
- Patients who have had treatment with immuno-suppressive medicines, following kidney transplant.

4.2 Posology and method of administration

Posology

Doses are expressed in terms of the base.

The total daily dose by any route should not normally exceed 2,4 g.

Adults:

Intravenous injection

- The usual dose by intravenous injection is 200 mg.
- It should be given ***slowly*** over at least 2 minutes.
- Rapid intravenous injection may be associated with cardiac arrest and arrhythmias (see section 4.4).
- It may be repeated every 4 to 6 hours.
- If a larger dose is required, or if the patient has cardiovascular impairment, intravenous infusion is recommended (see section 4.4).

Intravenous infusion

- For an intermittent intravenous infusion, the recommended dose is 400 mg (in 100 ml of sodium chloride 0,9 %), given over 30 minutes to 1 hour and repeated every 4 to 6 hours is necessary.
- For a continuous intravenous infusion, the recommended rate is 50 to 100 mg per hour.
- Prepared infusion must be stored in a refrigerator at ± 4 °C.

Intramuscular injection:

The usual intramuscular dose is 200 mg which may be repeated at intervals of 4 to 6 hours.

Special populations

Patients with impaired renal function

- The dosage of PHARMA-Q CIMETIDINE INJECTION should be reduced in patients with impaired renal function (see section 4.4).
- Suggested reduction in doses should be according to creatinine clearance.
  - If the creatinine clearance is 0 to 15 ml per minute, the suggested dose is 200 mg twice daily.
  - If the creatinine clearance is 15 to 30 ml per minute, the suggested dose is 200 mg three times daily.
  - If the creatinine clearance is 30 to 50 ml per minute, the suggested dose is 200 mg four times daily.
  - If the creatinine clearance is over 50 ml per minute, then normal dosages should be used.

Elderly

The normal adult dosage may be used unless renal function is markedly impaired.

Paediatric population

Children

Clinical experience in children is limited. Therefore, PHARMA-Q CIMETIDINE INJECTION therapy cannot be recommended in children. In limited experience, 20 to 40 mg/kg per day has been administered in divided doses orally or parenterally. There is no evidence of clinical use in babies and PHARMA-Q CIMETIDINE INJECTION should therefore not be given to infants under one year of age (see section 4.3).

Method of administration

Cimetidine as in PHARMA-Q CIMETIDINE INJECTION may be given by the

intravenous or intramuscular routes.

4.3 Contraindications

PHARMA-Q CIMETIDINE INJECTION is contraindicated in:

- Patients who are hypersensitive to cimetidine or to any of the excipients (see section 6.1).
- Patients who are under one year of age).
- Patients who are pregnant or lactating as the safety in pregnancy and lactation has not been established.

4.4 Special warnings and precautions for use

PHARMA-Q CIMETIDINE INJECTION

Before giving this injection to patients with gastric ulcers, the possibility of malignancy should be excluded since **PHARMA-Q CIMETIDINE INJECTION** may mask the symptoms and allow transient healing of gastric cancer and delay diagnoses.

- Dosages should be reduced in patients with impaired renal function according to their creatinine clearance.
- Rapid intravenous injection should be avoided, as it may lead to cardiac arrest, dysrhythmias and transient hypotension in critically ill patients.
- Intravenous infusion is recommended in patients with cardiovascular involvement.
- There may be an increased risk of developing community acquired pneumonia in patients who are elderly, patients with chronic lung disease, diabetic or immunocompromised patients.
- Due to possible interaction with coumarins, close monitoring of prothrombin time is recommended when cimetidine is concurrently used.

- Co-administration of therapeutic medicines with a narrow therapeutic index, such as phenytoin or theophylline, may require dosage adjustment when starting or stopping concomitantly administered cimetidine (see Section 4.5).
- Intravenous injections should be given slowly, and intravenous infusion is recommended in patients with cardiovascular impairment

4.5 Interaction with other medicines and other forms of interaction

Cimetidine binds to cytochrome P450 and may inhibit the hepatic metabolism of many medicines.

This may prolong the elimination of medicines which are metabolised by oxidation in the liver and cause increases in their plasma concentrations. Although many interactions may occur, only few are clinically significant; particularly those which have a narrow therapeutic index where the risk of toxicity may require a dosage adjustment.

Significant or potentially significant interactions occur with:

- Anti-dysrhythmic medicines such as lignocaine and procainamide.
- Anti-epileptics such as phenytoin and carbamazepine.
- Oral sulphonylurea antidiabetics such as glipizide.
- Warfarin and other oral anti-coagulants.
- Tricyclic antidepressants such as amitriptyline.
- Calcium channel blockers such as nifedipine.
- Ciclosporin.
- Chloramphenicol.
- Chlorpromazine.
- Theophylline.
- Suxamethonium.
- Pethidine.

Close monitoring of plasma concentrations is required, and dosage adjustment may be necessary.

Interactions may occur by several mechanisms including:

- Competition for renal tubular secretion; This may result in increased plasma levels of certain medicines including procainamide, metformin, ciclosporin and tacrolimus.
- Alteration of gastric pH; The bioavailability of certain medicines may be affected. This can result in either an increase in absorption (e.g., atazanavir) or a decrease in absorption (e.g., some azole antifungals such as ketoconazole, itraconazole or posaconazole).
- Unknown mechanisms: Cimetidine may potentiate the myelosuppressive effects (e.g., neutropenia, agranulocytosis) of chemotherapeutic medicines such as carmustine, fluorouracil, epirubicin, or therapies such as radiation. Data shows that isolated cases of clinically relevant interactions have been documented with narcotic analgesics (e.g., morphine).

Cimetidine as in PHARMA-Q CIMETIDINE INJECTION reduces gastric acid and secretion and can therefor impair absorption of iron from the gastro-intestinal tract. It is also associated with malabsorption of protein-bound vitamin $B_{12.}$ The risk of deficiency anaemias during long-term therapy cannot be excluded. In view of a report that glucose handling was impaired after long-term cimetidine administration, caution should be observed in the treatment of diabetics or elderly patients with cimetidine as in PHARMA-Q CIMETIDINE INJECTION.

4.6 Fertility, pregnancy and lactation

PHARMA-Q CIMETIDINE INJECTION is contra-indicated for use:

- During pregnancy and lactation as the safety in pregnancy and lactation has not been established (see section 4.3).

Breastfeeding

Cimetidine crosses the placental barrier and is excreted into breast milk.

4.7 Effects on ability to drive and use machines

Patients should be instructed that they should avoid potentially hazardous tasks such as driving and operating machinery until they know how PHARMA-Q CIMETIDINE INJECTION affects them.

4.8 Undesirable effects

a. Summary of the safety profile

PHARMA-Q CIMETIDINE INJECTION may have side effects although not everyone gets them.

b. Tabulated summary of adverse reactions

The frequency of adverse reactions listed below is defined using the following convention: frequent; less frequent or frequency unknown (cannot be estimated from the available data).

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Agranulocytosis, neutropenia, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia.
Immune system disorders	Less frequent	Anaphylaxis

MedDRA system organ class	**Frequency**	**Adverse reactions**
Psychiatric disorders	Less frequent	Depression, hallucinations and reversible confusional states, especially in the elderly or in seriously ill patients such as those with renal failure.
Nervous system disorders	Frequent	Headache, dizziness.
Cardiac disorders	Less frequent	Tachycardia, sinus bradycardia and heart block.
Gastrointestinal disorders	Frequent	Diarrhoea.
	Less frequent	Pancreatitis.
Hepato-biliary disorders	Less frequent	Hepatotoxicity, hepatitis and increases in serum transaminase levels.
Skin and subcutaneous tissue disorders	Frequent	Skin rashes.
	Less frequent	Reversible alopecia and hypersensitivity reactions.
Musculoskeletal and connective tissue disorders	Frequent	Myalgia.
	Less frequent	Arthralgia.
Renal and urinary disorders	Less frequent	Increases in plasma creatinine and interstitial nephritis.
Reproductive system and breast disorders	Less frequent	Gynaecomastia, reversible impotence in men, galactorrhoea
General disorders and	Frequent	Tiredness.

MedDRA system organ class	Frequency	Adverse reactions
administration site conditions	Less frequent	Fever.

c. Description of selected adverse reactions

Anaphylaxis is usually cleared on withdrawal of the medicine.

Interstitial nephritis cleared on withdrawal of the medicine. Small increases in plasma creatinine have been reported, unassociated with changes in glomerular filtration rate. The increases do not progress with continued therapy and disappear at the end of therapy.

Cimetidine as in PHARMA-Q CIMETIDINE INJECTION has a weak anti-androgenic effect and gynaecomastia, and reversible impotence in men receiving relatively high doses for conditions such as Zollinger-Ellison syndrome and galactorrhoea, have occurred. However, at regular dosage, the incidence is similar to that in the general population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

PHARMA-Q CIMETIDINE INJECTION 200 mg/2 ml overdose:

- Treatment is supportive and symptomatic.

- Dialysis may be necessary in cases where renal failure is present.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A11.4.3 Medicines acting on the gastro-intestinal tract.

ATC code: A02BA01.

Cimetidine is a selective, dose-dependent, reversible histamine H_2- receptor antagonist. Its main action is to inhibit gastric acid secretion and it reduces the output of pepsin. It also competitively inhibits the other actions of histamine which are mediated by H_2-receptors. The decrease in gastric acid secretion occurs regardless of the nature of the physiological stimulus to secretion, i.e., both basal (fasting) and nocturnal acid secretion, are reduced. Both the volume of secretion and the concentration of acid and pepsin in the secretion are reduced. It also inhibits gastric secretion elicited by muscarinic agonists or by gastrin.

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 H_2 blockers to suppress responses to all three physiological secretagogues makes them potent inhibitors of all phases of gastric acid secretion. Thus, these medicines will inhibit basal (fasting) secretion and nocturnal secretion and also that stimulated by food, sham feeding, fundic distension, insulin, or caffeine. The H_2 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.

5.2 Pharmacokinetic properties

Absorption

Cimetidine is rapidly and virtually completely absorbed. Absorption is little impaired by food or by antacids.

Distribution

Peak concentrations in plasma are attained in about 1 to 2 hours.

Biotransformation

Hepatic first-pass metabolism results in bioavailability of about 60 % for cimetidine.

Elimination

The half-time for elimination of cimetidine is 2 – 3 hours. To a large extend it is excreted in the urine without being metabolised. Small amounts are recovered in the stool.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (37 % *m/m*)

Water for injections

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Keep ampoule in container until required for administration.

Store at or below 25 °C.

Protect from light.

6.5 Nature and contents of container

2 ml clear, type 1, colourless ampoules ~~in~~

Pack size: containers of 10 or 100 ampoules.

6.6 Special precautions for disposal and other handling

None known

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMA-Q HOLDINGS (Pty) Ltd.

50 Commando Road

Industria West, 2093

Johannesburg

8 REGISTRATION NUMBER

32/11.4.3/0196

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Original date of registration: 13 November 2002

10 DATE OF REVISION OF THE TEXT

29 August 2022