Approved Professional Information for BIO CIMETIDINE 200 & 400

SCHEDULING STATUS

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1. NAME OF THE MEDICINE

BIO CIMETIDINE 200 film-coated tablets

BIO CIMETIDINE 400 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each BIO CIMETIDINE 200 film-coated tablet contains 200 mg cimetidine.

Each BIO CIMETIDINE 400 film-coated tablet contains 400 mg cimetidine.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

BIO CIMETIDINE 200 tablets are white, biconvex round film-coated tablets.

BIO CIMETIDINE 400 tablets are white bar-shaped biconvex film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BIO CIMETIDINE is indicated in:

- The treatment of duodenal and benign gastric ulceration and peptic oesophagitis, recurrent ulceration, stomal ulceration and other conditions where reduction of gastric acid secretion has been shown to be beneficial.
- Maintenance therapy for periods of up to one year in those patients with recurrence of

duodenal ulceration after short-term therapy.

- The management of those patients who are at high risk from haemorrhage of the upper-intestinal tract due to hepatic failure and treatment with immunosuppressive medicines, following kidney transplant.
- Management of pathological hypersecretion such as Zollinger-Ellison syndrome, systemic mastocytosis, multiple endocrine adenomas.
- Erosive gastro-oesophageal reflux disease (GORD).

4.2 Posology and method of administration

Posology

Duodenal and gastric ulcers

A single dose of 800 mg daily taken at bedtime, for 4 weeks in the case of duodenal ulcer and 6 weeks for a gastric ulcer. Where appropriate, a maintenance dose of 400 mg at bedtime or 200 mg twice daily should be taken for a period up to a year.

Oesophageal reflux

A dose of 400 mg four times daily (with meals and at bedtime) for 4 – 8 weeks is recommended.

Zollinger-Ellison syndrome

A dose of 400 mg four times daily (with meals and at bedtime) for 4 – 8 weeks is recommended. This dose can be increased to a maximum of 2,4 g per day, if necessary.

Maintenance treatment: Prophylaxis of recurrent ulcer

400 mg at bedtime or increase to 400 mg twice a day, if necessary for up to one year.

Special populations

The dose of BIO CIMETIDINE should be reduced in patients with impaired renal function (see section 4.4).

Paediatric population

Safety and/or efficacy of BIO CIMETIDINE in children have not been established.

Method of administration

BIO CIMETIDINE may be given by mouth or the nasogastric route, and the total daily dose should not exceed 2,4 g. When BIO CIMETIDINE is given orally, the daytime doses should be taken with meals.

4.3 Contraindications

- Patients with a known hypersensitivity to cimetidine or to any of the excipients (see section 6.1).
- Pregnancy and breastfeeding.

4.4 Special warnings and precautions for use

The dosage of BIO CIMETIDINE should be reduced in patients with impaired renal function according to creatinine clearance. Suggested doses according to creatinine clearance are creatinine clearance of 0 – 15 L per minute, 200 mg twice daily; 15 – 30 mL per minute, 200 mg three times daily; 30 – 50 mL per minute, 200 mg four times daily; over 50 mL per minute, normal dosage.

Before giving BIO CIMETIDINE to patients with gastric ulcer, the possibility of malignancy should be excluded by endoscopy and biopsy, if possible, because BIO CIMETIDINE can relieve the symptoms and help the superficial healing of the gastric cancer. The consequences of potential delay in diagnosis should be borne in mind especially in middle aged patients or over, with new or recently changed dyspeptic symptoms.

Care should be taken that patients with a history of peptic ulcer, particularly the elderly, being treated with BIO CIMETIDINE and a non-steroidal anti-inflammatory drug (NSAID) are observed

regularly.

Due to possible interaction with coumarins (e.g. warfarin), close monitoring of prothrombin time is recommended when BIO CIMETIDINE is concurrently used (see section 4.5).

Co-administration of medicines with a narrow therapeutic index, such as phenytoin or theophylline, may require dosage adjustment when starting or stopping concomitantly administered BIO CIMETIDINE (see section 4.5).

BIO CIMETIDINE contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially sodium free.

4.5 Interaction with other medicines and other forms of interaction

BIO CIMETIDINE can prolong the elimination of medicines metabolised by oxidation in the liver. Close monitoring of patients on BIO CIMETIDINE receiving oral anticoagulants (e.g. warfarin) or phenytoin is recommended and a reduction in the dosage of these medicines may be necessary. In patients on treatment or with illnesses that could cause falls in blood cell count, the possibility that H_2-receptor antagonism could potentiate this effect should be borne in mind.

BIO CIMETIDINE has the potential to affect absorption, metabolism or renal excretion of other medicines which is particularly important when medicines with a narrow therapeutic index are administered concurrently. The altered pharmacokinetics may necessitate dosage adjustment of the affected medicine or discontinuation of treatment (see section 4.4).

Interactions may occur by several mechanisms including:

- BIO CIMETIDINE inhibits the activity of cytochrome P450 in the liver, thereby slowing the hepatic metabolism of many medicines. Inhibition of certain cytochrome P450 enzymes (including CYP1A2, CYP2C9, CYP2D6 and CYP3A3/A4, and CYP2C18) may result in

increased plasma levels of certain medicines, including warfarin-type coumarin anticoagulants (e.g. warfarin), tricyclic antidepressants (e.g. amitriptyline), class I antiarrhythmics (e.g. lidocaine (lignocaine)), calcium channel blockers (e.g. nifedipine, diltiazem), oral sulfonylureas (e.g. glipizide), phenytoin, suxamethonium, theophylline and metoprolol.

- 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: BIO CIMETIDINE may potentiate the myelosuppressive effects (e.g. neutropenia, agranulocytosis) of chemotherapeutic medicines such as carmustine, fluorouracil, epirubicin, or therapies such as radiation. Isolated cases of clinically relevant interactions have been documented with narcotic analgesics (e.g. morphine).

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and breastfeeding have not been established.

Although tests in animals and clinical evidence have not revealed any hazards from the administration of cimetidine, as contained in BIO CIMETIDINE, during pregnancy or breastfeeding, both animal and human studies have shown that it does cross the placental barrier and is excreted in breast milk. BIO CIMETIDINE should not be used during pregnancy and breastfeeding.

4.7 Effects on ability to drive and use machines

Confusion, headache and dizziness have been reported with BIO CIMETIDINE (see section 4.8).

Patients should not drive or use machines until it has been established that BIO CIMETIDINE does not affect their ability to do so safely.

4.8 Undesirable effects

Blood and lymphatic system disorders

Less frequent: Leucopenia, thrombocytopenia, aplastic anaemia, pancytopenia and agranulocytosis or neutropenia.

Immune system disorders

Less frequent: Hypersensitivity reactions, anaphylaxis. Anaphylaxis is usually cleared on withdrawal of the medicine.

Psychiatric disorders

Less frequent: Depression, confusion, hallucinations. Confusional states, reversible within a few days of withdrawing cimetidine as contained in BIO CIMETIDINE, have been reported, usually in elderly or 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. Pancreatitis cleared on withdrawal of the medicine.

Hepatobiliary disorders

Less frequent: Hepatitis, increased serum transaminase levels, hepatotoxicity. Hepatitis and increased serum transaminase levels cleared on withdrawal of the medicine.

Skin and subcutaneous tissue disorders

Frequent: Skin rashes.

Less frequent: Reversible alopecia and hypersensitivity vasculitis. Hypersensitivity vasculitis usually cleared on withdrawal of the medicine.

Musculoskeletal and connective tissue disorders

Frequent: Myalgia.

Less frequent: Arthralgia.

Renal and urinary disorders

Less frequent: Increases in plasma creatinine and interstitial nephritis. 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.

Reproductive system and breast disorders

Less frequent: Gynaecomastia and reversible impotence. Gynaecomastia is usually reversible upon discontinuation of cimetidine therapy. Reversible impotence has been reported particularly in patients receiving high doses (e.g. in Zollinger-Ellison syndrome). However, at regular dosage, the incidence is similar to that in the general population. Galactorrhoea.

General disorders and administrative site conditions

Frequent: Tiredness.

Less frequent: Fever. Fever cleared on withdrawal of the medicine.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of BIO CIMETIDINE is important. It allows continued monitoring of the benefit/risk balance of BIO CIMETIDINE. 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

Symptoms of overdose

Acute overdosage of up to 20 grams has been reported several times with no significant ill effects.

Management

Treatment of overdosage should consist of emesis, if ingestion occurred not more than four hours before, followed by symptomatic and supportive measures only.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 11.4.3 Antacids, other.

Pharmacotherapeutic group: H_2-receptor antagonists.

ATC code: A02BA01.

Cimetidine is a histamine H_2-receptor antagonist and accordingly it rapidly inhibits both stimulated and basal gastric acid secretion of acid and reduces pepsin output. It is a reversible, competitive antagonist and is used as an anti-ulcer medicine. It is highly selective in its action, is virtually without effect on H_1-receptors, or indeed on receptors for other autocoids or medicines. Despite the widespread distribution of H_2-receptors in the body, cimetidine interferes remarkably little with physiological functions other than gastric secretion, implying that the extragastric H_2-receptors are of minor physiological importance.

However, H_2-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 H_2-agonists in a dose-

dependent, competitive manner; the degree of inhibition parallels the plasma concentration of the medicine over a wide range. In addition, the H_2-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 acetylcholine (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 H_2-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

Absorption

Cimetidine is readily and virtually completely absorbed from the gastrointestinal tract and peak plasma concentrations are obtained about an hour after administration on an empty stomach. Food delays the rate of absorption with the peak plasma concentration occurring after about 2 hours. The duration of action is reported to be prolonged by administration with food.

Distribution

Cimetidine does not readily cross the blood-brain barrier.

Biotransformation

Cimetidine is only partially metabolised in the liver. Hepatic first-pass metabolism results in a bioavailability of about 60 % for cimetidine.

Elimination

The elimination half-life is about two to three hours and increases with renal impairment. 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 stools.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal silicone dioxide (Aerosil 200)

Corn starch/maize starch (Super Sonic)

Magnesium stearate

Microcrystalline cellulose (Arbocel type A 300)

Povidone K25 (Plasodone K-25)

Sodium lauryl sulphate (Vinapol-90P)

Sodium starch glycolate (Primojel).

Coating

Opadry 03F58792 White (consisting of HPMC 2910/hypromellose (E464), macrogol/PEG (E1521) and titanium dioxide (E171))

Purified talcum.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C, protect from light.

6.5 Nature and contents of container

Blister strips (10 tablets per strip) with clear, colourless polyvinylchloride (PVC) moulded to accept one tablet per pocket and sealed with soft, matte, silver, printed aluminium foil. Strips are packed into cartons with a patient information leaflet.

BIO CIMETIDINE 200 pack sizes: 60 and 150 tablets.

BIO CIMETIDINE 400 pack sizes: 60 and tablets.

Securitainer (polypropylene) containing tablets and patient information leaflet. Sealed with a securitainer snap-on cap (polyethylene) and labelled with a glossy adhesive printed label.

BIO CIMETIDINE 200 pack sizes: 60 and 150 tablets.

BIO CIMETIDINE 400 pack sizes: 60 and 500 tablets.

HDPE containers containing tablets and patient information leaflet. 100 cc white opaque HDPE container with white opaque screw cap and induction sealing wad.

BIO CIMETIDINE 200 pack sizes: 60 and 150 tablets.

BIO CIMETIDINE 400 pack sizes: 60 and tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor, Block K West, Central Park

400 16th Road, Randjespark, Midrand 1685

South Africa

8. REGISTRATION NUMBERS

BIO CIMETIDINE 200: 31/11.4.3/0679

BIO CIMETIDINE 400: 31/11.4.3/0680

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 14 July 1999

10. DATE OF REVISION OF THE TEXT

28 March 2024

1.3.1.1.1 - Approved PI - 0007