National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

Summary of product characterization (SMPC)

For

Cimetidine 400mg Tablet

1. **Name of the medicinal product**
   Cimetidine 400mg Tablet

2. **Qualitative and quantitative composition**
   Each tablet contains 400mg cimetidine.

3. **Pharmaceutical form**
   Tablet.

4. **Clinical particulars**

4.1. Therapeutic indications

Cimetidine 400mg is a histamine H2-receptor antagonist which rapidly inhibits both basal and stimulated gastric secretion of acid and reduces pepsin output. Cimetidine is indicated in the treatment of duodenal and benign gastric ulceration, including that associated with non-steroidal anti-inflammatory agents, recurrent and stomal ulceration , oesophageal reflux disease and other conditions where reduction of gastric acid by Cimetidine has been shown to be beneficial: persistent dyspeptic symptoms with or without ulceration, particularly meal-related upper abdominal pain, including such symptoms associated with non-steroidal anti-inflammatory agents; the prophylaxis of gastrointestinal haemorrhage from stress ulceration in seriously ill patients ; before general anaesthesia in patients thought to be at risk of acid aspiration (Mendelson's Syndrome), particularly obstetric patients during labour ; to reduce malabsorption and fluid loss in the short bowel syndrome; and in pancreatic insufficiency to reduce degradation of enzyme supplements. Cimetidine is also recommended in the management of the Zollinger-Ellison syndrome.

4.2. Posology and method of administration

The total daily dose by any route should not normally exceed 2.4g. Dosage should be reduced in patients with impaired renal function (see Special warnings and precautions for use)

Posology

Adults:

Oral: The usual dosage is 400mg twice a day, with breakfast and at bedtime. For patients with duodenal or benign gastric ulceration, a single daily dose of 800mg at bedtime is recommended. Other effective regimens are 200mg three times a day with meals and 400mg at bedtime (1.0g/day) and, if inadequate, 400mg four times a day (1.6g/day), also with meals and at bedtime.

Symptomatic relief is usually rapid. Treatment should be given initially for at least four weeks (six weeks in benign gastric ulcer, eight weeks in ulcer associated with continued non-steroidal anti-inflammatory agents) even if symptomatic relief has been achieved sooner. Most ulcers will have healed by that stage, but those which have not will usually do so after a further course of treatment. Treatment may be continued for longer periods in those patients who may benefit from reduction of gastric secretion and the dosage may be reduced as appropriate to 400mg at bedtime or 400mg in the morning and at bedtime. In patients with benign peptic ulcer disease who have responded to the initial course, relapse may be prevented by continued treatment, usually with 400mg at bedtime; 400mg in the morning and at bedtime has also been used.

In oesophageal reflux disease, 400 mg four times a day, with meals and at bedtime,for four to eight weeks is recommended to heal oesophagitis and relieve associated symptoms. In patients with very high gastric acid secretion (e.g. Zollinger-Ellison syndrome) it may be necessary to increase the dose to 400mg four times a day or in occasional cases further. Since

Cimetidine may not give immediate symptomatic relief, antacids can be made available to all patients until symptoms disappear.
In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients, doses of 200 - 400mg can be given every four to six hours by the oral route.
In patients thought to be at risk of acid aspiration syndrome, an oral dose of 400mg can be given 90-120 minutes before induction of general anaesthesia or, in obstetric practice, at the start of labour. While such a risk persists, a dose of up to 400mg may be repeated (parenterally if appropriate) at four hourly intervals as required up to the usual daily maximum of 2.4g. Cimetidine should not be used. The usual precautions to avoid acid aspiration should be taken.
In the short bowel-syndrome e.g. following substantial resection for Crohn's disease, the usual dosage range (see above) can be used according to individual response.
To reduce degradation of pancreatic enzyme supplements, 800-1600mg a day may be given, according to response, in four divided doses, one to one and a half hours before meals.

Elderly:
The normal adult dosage may be used unless renal function is markedly impaired. (see section 4.4).

Paediatric population:
Experience in children is less than that in adults. In children more than one year old, Cimetidine 25-30mg/kg body weight per day in divided doses may be administered by oral route. The use of Cimetidine in infants under one year old is not fully evaluated, 20mg/kg body weight per day in divided doses has been used.

Method of administration
For oral administration.

4.3 Contraindications
Hypersensitivity to Cimetidine or to any other of the tablet ingredients listed. (see section 6.1).

4.4 Special warnings and precautions for use
Dosage should be reduced in patients with impaired renal function according to creatinine clearance.
The following doses are suggested: Creatinine clearance of 0 to l5ml per minute, 200mg twice a day; 15 to 30ml per minute, 200mg three times a day; 30 to 50ml per minute, 200mg four times a day; over 50 ml per minute, normal dosage. Cimetidine is removed by haemodialysis, but not to any significant extent by peritoneal dialysis.
Clinical trials over six years' continuous treatment and more than 15 years' widespread use have not revealed unexpected adverse reactions related to long-term therapy.
The safety of prolonged use is not fully established and care should be taken to observe periodically patients given prolonged treatment.
Care should be taken that patients with a history of peptic ulcer, particularly the elderly, being treated with Cimetidine and a non-steroidal anti-inflammatory agent are observed regularly. Before initiating therapy with this preparation for any gastric ulceration, malignancy should be excluded by endoscopy and biopsy, if possible, because Cimetidine tablets 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.

Due to possible interaction with coumarins, close monitoring of prothrombin time is recommended when cimetidine is concurrently used.
Co-administration of therapeutic agents 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).

4.5 Interaction with other medicinal products and other forms of interaction

Cimetidine can prolong the elimination of drugs metabolised by oxidation in the liver. Although pharmacological interactions with a number of drugs, e.g. Diazepam, Propranolol, have been demonstrated, only those with oral anticoagulants, phenytoin, theophylline and intravenous lidocaine appear, to date, to be of clinical significance. Close monitoring of patients on Cimetidine receiving oral anticoagulants or phenytoin is recommended and a reduction in the dosage of these drugs may be necessary.
In patients on drug treatment or with illnesses that could cause falls in blood cell count, the possibility that H2 -receptor antagonism could potentiate this effect should be borne in mind.
Cimetidine has the potential to affect the absorption, metabolism or renal excretion of other drugs which is particularly important when drugs with a narrow therapeutic index are administered concurrently. The altered pharmacokinetics may necessitate dosage adjustment of the affected drug or discontinuation of treatment (see Section 4.4).
Interactions may occur by several mechanisms including:

1) Inhibition of certain cytochrome P450 enzymes (including CYP1A2, CYP2C9, CYP2D6 and CYP3A3/A4, and CYP2C18); Inhibition of these enzymes may result in increased plasma levels of certain drugs including warfarin-type coumarin anticoagulants (e.g. warfarin), tricyclic antidepressants (e.g. amitriptyline), class I antiarrhythmics (e.g. lidocaine), calcium channel blockers (e.g. nifedipine, diltiazem), oral sulfonylureas (e.g. glipizide), phenytoin, theophylline and metoprolol.
2) Competition for renal tubular secretion; This may result in increased plasma levels of certain drugs including procainamide, metformin, ciclosporin and tacrolimus.

3) Alteration of gastric pH; The bioavailability of certain drugs 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).

4) Unknown mechanisms; Cimetidine may potentiate the myelosuppressive effects (e.g. neutropenia, agranulocytosis) of chemotherapeutic agents 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

Although tests in animals and clinical evidence have not revealed any hazards from the administration of Cimetidine during pregnancy or lactation, both animal and human studies have shown that it does cross the placental barrier and is excreted in breast milk. As with most drugs, the use of Cimetidine should be avoided during pregnancy and lactation unless essential.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Adverse experiences with Cimetidine are listed below by system organ class and frequency. Frequencies are defined as: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000,
<1/100), rare (>1/10000, <1/1000), very rare (<1/10000).

Blood and Lymphatic system disorders:

Uncommon: Leukopenia
Rare: Thrombocytopenia, aplastic anaemia
Very rare: Pancytopenia, agranulocytosis

Immune system disorders:

Very rare: Anaphylaxis. Anaphylaxis is usually cleared on withdrawal of the drug.

Psychiatric disorders

Uncommon: Depression, confusional states, hallucinations. Confusional states, reversible within a few days of withdrawing Cimetidine, have been reported, usually in elderly or ill patients.

Nervous system disorders

Common: Headache, dizziness

Cardiac disorders

Uncommon: Tachycardia
Rare: Sinus bradycardia
Very rare: Heart block

Gastrointestinal disorders

Common: Diarrhoea
Very rare: Pancreatitis. Pancreatitis cleared on withdrawal of the drug.

Hepatobiliary disorders

Uncommon: Hepatitis
Rare: Increased serum transaminase levels. Hepatitis and increased serum transaminase levels
cleared on withdrawal of the drug.

Skin and subcutaneous tissue disorders

Common: Skin rashes
Very rare: Reversible alopecia and hypersensitivity vasculitis. Hypersensitivity vasculitis usually
cleared on withdrawal of the drug.

Musculoskeletal and connective tissue disorders

Common: Myalgia
Very rare: Arthralgia

Renal and urinary disorders

Uncommon: Increases in plasma creatinine
Rare: Interstitial nephritis. Interstitial nephritis cleared on withdrawal of the drug. 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

Uncommon: 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.
Very rare: Galactorrhoea

General disorders and administration site conditions
Common: Tiredness
Very rare: Fever. Fever cleared on withdrawal of the drug.

4.9 Overdose
Acute over dosage of up to 20 grams has been reported several times with no significant ill effects. Induction of vomiting and/or gastric lavage may be employed together with symptomatic and supportive therapy.

5. Pharmacological properties
5.1 Pharmacodynamics 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.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. Pharmaceutical particulars

6.1 List of excipients*:*

Maize Starch
Magnesium Stearate
Povidone (K30)
Sodium starch glycollate
Aerosil 200

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Blister: Do not store above 30°C.
Store in the original package.
Keep the container in the outer carton.

6.5 Nature and contents of container

Blister (PVC/aluminum foil blister strips in a carton): 20 tablets

6.6 Special precautions for disposal and other handling

Nothing stated.

7. Marketing authorization holder

Distributed by
UCGOD Pharmaceutical Limited.
6, Oba T.T, Dada Avenue, Dental Bus Stop
Alonge Idi-Iroko Road, Ota Ogun State, Nigeria.

Manufactured by
Daily Sun Pharmaceutical Company Limited
Plot 3 & 4 Tomori industrial estate, off Idiroko road, Sango Ota, Ogun state.