SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cimetidine Tablets BP 800mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 800mg cimetidine BP.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pale green, oval, film coated tablets, embossed with C3 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cimetidine Tablets are indicated for the following.

a) The treatment of duodenal and benign gastric ulceration, and oesophageal reflux disease.

b) The treatment of persistent dyspeptic symptoms with or without ulceration, particularly meal-related upper abdominal pain.

c) The prophylaxis of gastro-intestinal haemorrhage from stress ulceration in seriously ill patients.

d) Before general anaesthesia in patients thought to be at risk of acid aspiration (Mendelson's) syndrome, particularly obstetric patients during labour.

e) To reduce malabsorption and fluid loss in short bowel syndrome.

f) To reduce degradation of enzyme supplements in pancreatic

insufficiency. g) In the management of Zollinger-Ellison syndrome.

4.2 Posology and method of administration

The total daily dose should not normally exceed 2.4g. Dosage should be
reduced in patients with impaired renal function (see section 4.4).

Posology

Adults: The usual dosage is 400mg twice a day with breakfast and at bedtime. Alternatively, for patients with duodenal or benign gastric ulceration, a single daily dose of 800mg at bedtime is recommended. Other effective regimens are 200mg, 3 times a day with meals and 400mg at bedtime (1.0g/day) and, if inadequate, 400mg, 4 times a day (1.6g/day), also with meals and at bedtime.

Treatment should be given initially for at least 4 weeks (6 weeks in benign gastric ulcer) 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, in those who have responded to treatment, for example 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, 400mg 4 times a day, with meals and at bedtime, for 4 to 8 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 4 times a day, or in occasional cases further.

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 200mg-400mg can be given every 4 to 6 hours.

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 at 4 hourly intervals, as required, up to the usual daily maximum of 2.4g. 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, 800mg-1,600mg a day may be given according to response in 4 divided doses, 1 to 1½ 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 25mg-30mg/kg body weight per day in divided doses may be administered. The use of cimetidine in infants under one year old has not yet been fully evaluated; 20mg/kg body weight per day in divided doses has been used.

Patients with impaired renal function: dosage should be reduced in patients with impaired renal function according to creatinine clearance. The following dosages are suggested:

Creatinine clearance	**Cimetidine dosage**
0 to 15ml per minute	200mg, twice a day
15ml to 30ml per minute	200mg, 3 times a day
30ml to 50ml per minute	200mg, 4 times a
day over 50ml per minute	normal dosage.

Method of administration:
For oral use. The tablets should be swallowed with a drink of water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in 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 dosages are suggested: creatinine clearance of 0-15ml 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 50ml per minute, normal dosage.

Cimetidine is removed by haemodialysis, but not to any significant extent by peritoneal dialysis.

Clinical trials of 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).

This medicine contains less than 1mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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 between cimetidine and a number of drugs have been demonstrated, e.g. diazepam and propranolol, only those with oral anticoagulants, phenytoin and 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 H_2-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. The use of this preparation during pregnancy and lactation should be avoided unless considered essential by the physician.

4.7 Effects on ability to drive and use machines

Patients should take care when driving, operating machinery or carrying out other activities which require full alertness if they feel dizzy, very tired and/or confused.

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 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google

Play or Apple App Store.

4.9 Overdose

Acute overdosage of up to 20g 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 Pharmacodynamic properties

Cimetidine, one of the H_2 blockers, is a reversible, competitive antagonist of the actions of histamine on H_2 receptors. It is highly selective in its action and is virtually without effect on H_1 receptors or, indeed, on receptors for other autacoids or drugs. The most prominent of the effects of histamine that are mediated by H_2 receptors is stimulation of gastric acid secretion and they interfere remarkably little with physiological functions other than gastric secretion.

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 drug 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 2 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 acetyl choline or gastrin when they act on their own discrete receptors. Receptors for all 3 secretagogues are present on the parietal cell. The ability of H_2 blockers to suppress responses to all 3 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 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

Cimetidine is rapidly and virtually completely absorbed. Absorption is little impaired by food or by antacids. Peak concentrations in plasma are attained in about 1 to 2 hours. Hepatic first-class metabolism results in a bioavailability of about 60% for cimetidine. The elimination half-life is about 2 to 3 hours. Cimetidine is eliminated primarily by the kidneys, and 60% or more may appear in the urine unchanged; much of the rest as oxidation products. Small amounts are recovered in the stool.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, povidone 30, sodium starch glycollate, sodium lauryl sulphate, colloidal silicon dioxide and magnesium stearate.

Film coating: hydroxypropyl methylcellulose (E464), polyethylene glycol, and colours: quinoline yellow aluminium lake (E104), indigo carmine aluminium lake (E132), titanium dioxide (E171) and iron oxide yellow (E172).

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

1) Polypropylene tubes with low density polyethylene caps. High density polyethylene film may be used as packing material.

   Pack sizes: 60, 100, 150 and 250 tablets.

2) Blister packs consisting of clear PVC and hard temper aluminium foil, contained in a carton.

   Pack size: 30 tablets.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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UK

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PL 55612/0029

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