**PRODUCT DESCRIPTION**

**Cimetidine (Tagamet®) 200mg Tablet:**
Each pale green, circular, biconvex, film coated tablets with ‘TAGAMET’ imprinted on one face and plain on the other contains 200mg Cimetidine.

**Cimetidine (Tagamet®) 400mg Tablet:**
Each pale green, capsule-shaped, film-coated tablets, debossed on one face with TAGAMET and 400 on the other contains 400mg Cimetidine.

**PHARMACOLOGIC PROPERTIES**

**Mechanism of Action**
- Cimetidine is a histamine H₂-receptor antagonist
- Competitively inhibits the action of histamine at the parietal cell histamine H₂-receptors
- Inhibits both the stimulated and basal secretion of gastric acid and reduces pepsin output
- Also has cytoprotective properties and therefore has a beneficial effect in maintaining the integrity of the gastric mucosal barrier.

**Pharmacokinetics**

**Absorption**
Cimetidine is rapidly absorbed after oral administration.

**Elimination**
Cimetidine is principally excreted in the urine and has a half-life of approximately 2 hours.

**INDICATIONS**

Cimetidine 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 gastro-intestinal haemorrhage 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.

**DOSAGE AND ADMINISTRATION**

Cimetidine is usually given orally, but parenteral or nasogastric dosing may be substituted for all or part of the recommended oral dose in cases where oral dosing is impracticable or considered inappropriate. The total daily dose by any route should not normally exceed 2.4 g. Dosage should be reduced in patients with impaired renal function (see Precautions).

**ADULTS**

**Oral:** For patients with duodenal or benign gastric ulceration, a single daily dose of 800 mg at bedtime is recommended. Otherwise the usual dosage is 400 mg twice a day with breakfast and at bedtime. Other effective regimens are 200 mg three times a day with meals and 400 mg at bedtime (1.0 g/day) and, if inadequate, 400 mg four times a day (1.6 g/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). Most ulcers will have healed by that stage, but those that 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 400 mg at bedtime or 400 mg in the morning and at bedtime.

**In patients with benign peptic ulcer disease, relapse may be prevented by continued treatment, usually with 400 mg at bedtime; 400 mg 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 400 mg four 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 200 - 400 mg can be given every four to six hours by oral, nasogastric or parenteral routes. By direct intravenous injection a dose of 200 mg should not be exceeded; see below.
In patients thought to be at risk of acid aspiration syndrome an oral dose of 400 mg 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 400 mg may be repeated (parenterally if appropriate) at four-hourly intervals as required up to the usual daily maximum of 2.4 g.

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, 800-1600 mg a day may be given according to response in four divided doses, one to one and a half hours before meals.

**Parenteral:** Cimetidine may be given intramuscularly or intravenously.

The dose by intramuscular injection is normally 200 mg which may be repeated at four to six-hourly intervals. The usual dosage for intravenous administration is 200-400 mg which may be repeated four to six-hourly.

If direct intravenous injection cannot be avoided, 200 mg should be given slowly over a period of not less than 5 minutes, and may be repeated four to six-hourly. Rapid intravenous injection has been associated with cardiac arrhythmias. If there is cardiovascular impairment, or if a larger dose is needed, the dose should be diluted and given over at least 10 minutes. In such cases infusion is preferable.

For intermittent intravenous infusion, the contents of one Cimetidine Infusion bag (containing cimetidine 400 mg in 100 ml 0.9% w/v sodium chloride) should be infused over 30 minutes to 1 hour, and may be repeated every four to six hours.

If continuous intravenous infusion is required, Cimetidine may be given at an average rate of 50 to 100 mg/hour over 24 hours.

**ELDERLY**

The normal adult dosage may be used unless renal function is markedly impaired (see Precautions and Adverse reactions).

**CHILDREN**

Experience in children is less than that in adults. In children more than one year old, Cimetidine 25-30 mg/kg body weight per day in divided doses may be administered by either the oral or parenteral route.

The use of Cimetidine in infants under one year old is not fully evaluated; 20 mg/kg body weight per day in divided doses has been used.

**CONTRAINDICATIONS**

Hypersensitivity to cimetidine or its excipients.

Inhibition of the renal cation transport system by cimetidine may result in elevated dofetilide plasma concentrations. This can lead to an increased risk of ventricular arrhythmias, including torsades de pointes. Co-administration of dofetilide and cimetidine is therefore contraindicated (see Interactions).

**WARNINGS AND PRECAUTIONS**

Dosage should be reduced in patients with impaired renal function according to creatinine clearance. The following dosages are suggested: creatinine clearance of 0 to 15 ml per minute, 200 mg twice a day; 15 to 30 ml per minute, 200 mg three times a day; 30 to 50 ml per minute, 200 mg four times a day; over 50 ml per minute, normal dosage.

Cimetidine can prolong the elimination of drugs metabolised by oxidation in the liver. 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.

Rapid intravenous injection of cimetidine (less than 5 minutes) should be avoided (see Dosage and administration).

Clinical trials of over six years' continuous treatment and more than fifteen years' widespread use have not revealed unexpected adverse reactions related to long-term therapy. The safety of prolonged use is not, however, fully established and care should be taken to observe periodically patients given prolonged treatment.

Cimetidine treatment can mask the symptoms and allow transient healing of gastric cancer. The potential delay in diagnosis should particularly be borne in mind in patients of middle age and 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 Cimetidine and a non-steroidal anti-inflammatory agent are observed regularly.

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.

In patients such as the elderly, persons with chronic lung disease, diabetes or the immunocompromised, there may be an increased risk of developing community acquired pneumonia. A large epidemiological study showed an increased risk of developing community acquired pneumonia in current users of H2 receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk increase of 1.63 (95% CI, 1.07-2.48).

Due to the 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 adjustments when starting or stopping concomitantly administered cimetidine (see Interactions).

**DRUG INTERACTIONS**

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 Warnings and Precautions).

Interactions may occur by several mechanisms including:

1) Inhibition of certain cytochrome P450 enzymes (including CYP1A2, CYP2C9, CYP2D6 and CYP3A3/A, and CYP2C19);

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, quinidine), calcium channel blockers (e.g. nifedipine, diltiazem), oral sulfonlureas (e.g. glipizide), phenytoin, theophylline, metoprolol, cyclosporine, tacrolimus and diazepam.
2) Inhibition of renal tubular secretion via organic cation transporter (OCT) proteins; This may result in increased plasma levels of certain drugs including procainamide, quinidine, metformin, and dofetilide (see Contraindications).

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).

**PREGNANCY AND LACTATION**

There has been limited experience to date with the use of Cimetidine in pregnant patients. Adequate human data on use in lactation are not available. 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 milk. As with most drugs, the use of Cimetidine should be avoided during pregnancy and lactation unless essential.

**ADVERSE 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 (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), very rare (<1/10,000).

**Blood and lymphatic system disorders**
Uncommon: Leukopenia
Rare: Thrombocytopenia, aplastic anaemia
Very rare: Pancytopenia, agranulocytosis

**Immune system disorders**
Very rare: Anaphylaxis
Anaphylaxis 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: Increases in serum transaminase levels
Hepatitis and increases in 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. These increases are due to inhibition of renal tubular secretion of creatinine and are not associated 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.

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

**OVERDOSAGE**

Acute overdosage 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.
STORAGE
Store at temperatures not exceeding 30°C.

AVAILABILITY
Cimetidine (Tagamet®) 200mg tablet: 10 tablets per blister (box of 50’s).
Cimetidine (Tagamet®) 400mg tablet: 10 tablets per blister (box of 60’s).

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep all medicines out of reach of children.

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