Magicul

Cimetidine

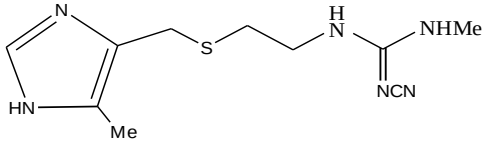
PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient: cimetidine.

Chemical name: 2-cyano-1-methyl-3-[2-(5-methylimidazol-4-yl-methylthio)ethyl]guanidine.

The structural formula for cimetidine is:



Molecular formula: $C_{10}H_{16}N_6S$ Molecular weight: 252.3

CAS Registry No.: 51481-61-9

DESCRIPTION

Cimetidine is an odourless white to off-white powder, which is sparingly soluble in water.

Each Magicul tablet contains 200 mg, 400 mg or 800 mg of cimetidine. The tablets also contain maize starch, povidone, microcrystalline cellulose, sodium starch glycollate (Type A), magnesium stearate, Opadry Green OY-8830 (ARTG no. 1538) for 200 mg and 800 mg tablets, and Opadry White Y-1-7000 E171 (ARTG no. 2731) for 400 mg tablets. *The tablets are gluten free*.

PHARMACOLOGY

Cimetidine is a histamine H_2-receptor antagonist. It was the first available agent that blocked the action of histamine at the histamine H_2-receptor site of the parietal cells and does so by competitive inhibition.

Pharmacologically, cimetidine does not exhibit classical anticholinergic effects. Studies have shown that cimetidine inhibits both daytime and nocturnal basal gastric acid secretion. Cimetidine also inhibits gastric acid secretion stimulated by food, histamine, pentagastrin, caffeine and insulin.

Animal pharmacology and toxicology

Cimetidine has been shown by *in vitro* studies to be a specific competitive H_2-receptor antagonist without significant interaction at catecholamine β-receptors, histamine H_1-receptors or muscarinic receptors. Its potency in terms of administered dose and in terms of blood concentrations achieved is very similar in man and in experimental animals. Thus, in all species studied, a blood concentration of about 2 micromol/L is associated with 50% inhibition of maximal acid output.

In chronic toxicity studies in dogs, some animals administered 504 mg/kg showed evidence of liver and kidney damage.

The kinetics of cimetidine and its absorption, metabolism and excretion are essentially similar in man, rat and dog.

Human pharmacology

Effect on basal (non-stimulated) acid secretion. In double blind, placebo controlled studies in duodenal ulcer patients, single doses of cimetidine markedly and consistently reduced fasting daytime and nocturnal basal gastric acid secretion in a dose related manner. Degree of inhibition was correlated with blood levels attained, at least 80%

inhibition usually being achieved when blood levels exceeded 0.5 mg/L. The time over which such levels were sustained varied among doses, the effect of a 200 mg dose diminishing after 4 to 5 hours and 300 mg after 7 to 8 hours, while 400 mg was still effective after 8 hours. The effect of cimetidine was due largely to significantly reduced acid concentration, but volume of gastric juice was reduced also. Gastric pH levels above 5 were seen regularly when effective blood levels were present, indicating that pepsin will be inactive for many periods during therapy.

Effect on stimulated acid secretion. Cimetidine was shown to be a potent inhibitor of gastric secretion stimulated by histamine, pentagastrin, insulin, food or caffeine in normal subjects and duodenal ulcer patients. At least 50% inhibition was associated with blood levels of 0.5 mg/L or more, while 80 to 90% inhibition usually occurred at blood levels above 1 mg/L. Timing of the dose relative to a test meal affected blood level patterns and hence pattern of response, the data suggesting that administration with meals provides optimum control of gastric secretion. Studies have shown that doses of 800 mg and 1 g per day will reduce 24 hour intragastric acidity by 70% and 72% respectively.

The effect of cimetidine on pepsin concentration was variable in these studies, but total pepsin output decreased as a result of the decrease in volume of gastric juice. As noted above, any pepsin secreted during periods when the pH is above 5 will be inactive.

Cimetidine significantly inhibited the histamine stimulated rise in intrinsic factor concentration, but did not affect the basal level of intrinsic factor.

In studies where serum gastrin was measured the expected rise in response to stimulants (food, etc.) was observed. In these studies, when gastric pH was controlled in both placebo and cimetidine groups, there was no difference in gastrin levels between the groups. However, when gastric pH was uncontrolled, the gastrin levels of the cimetidine groups were higher. This appears to be due to the higher gastric pH obtained with cimetidine.

Cimetidine has no effect on the rate of gastric emptying or on lower oesophageal sphincter (LOS) pressure.

Pharmacokinetics

Pharmacokinetic studies carried out in humans have demonstrated that cimetidine is well absorbed orally. Oral absorption studies carried out using a 200 mg dose have resulted in blood levels averaging 2.8 micromol/L (0.7 mg/L), occurring at times ranging from 45 to 75 minutes after dosing. Up to 34% of the drug was recovered from the urine 2 hours after dosing and after 24 hours 70% of the dose was accounted for.

Intravenous infusion of cimetidine labelled with ^{3}H in doses of 75 to 117 mg resulted in peak blood concentrations of 2 to 4.3 micromol/L (0.5 to 1.1 mg/L). The concentration of cimetidine in the blood declined with a half-life of 123 $\pm$ 12 minutes. Radioactivity in the urine confirmed rapid excretion by the kidney (60% in 2.5 hours), 70% being excreted unchanged and up to 19% as the sulphoxide.

Cimetidine is approximately 22% bound to human plasma protein.

INDICATIONS

- Short-term treatment of proven duodenal ulcer and gastric ulcer
- Maintenance treatment in those patients with recurrence of duodenal ulceration after short-term therapy
- Maintenance treatment for periods of up to one year to reduce the risk of relapse in patients with documented healing of chronic benign gastric ulcer
- Short-term treatment (no more than 12 weeks) of persistent gastro-oesophageal reflux disease,
- Short-term treatment of heartburn (up to two weeks) and other symptoms of gastro-oesophageal reflux disease.
- Treatment of gastrinoma (Zollinger-Ellison syndrome)
- Treatment of scleroderma oesophagus.

CONTRAINDICATIONS

Patients with known hypersensitivity to cimetidine or any other component of Magicul.

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. Coadministration of dofetilide and cimetidine is therefore contraindicated (see Interactions with Other Medicines).

PRECAUTIONS

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 H_2 receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk of 1.63% (055 Cl, 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 adjustment when starting or stopping concomitantly administered cimetidine (see **Interactions with Other Medicines**).

Gastric ulcer

Treatment with a histamine H_2-receptor antagonist may mask symptoms associated with carcinoma of the stomach and therefore may delay diagnosis of the condition. The potential delay in diagnosis should be borne in mind in patients of middle age or older with new or recently changed dyspeptic symptoms. Accordingly, where gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with cimetidine is instituted. It is then important to re-endoscope the patient after 8 to 12 weeks of cimetidine therapy to check that the ulcer has healed.

Gastro-oesophageal reflux disease

Treatment of persistent gastro-oesophageal reflux disease and associated symptoms of reflux should only be initiated if the condition is unresponsive to conservative reflux measures and simple drug therapies such as antacids. Treatment should be short term (no more than 12 weeks).

Patients with impaired renal function or undergoing haemodialysis

Dosage should be reduced according to creatinine clearance. For patients undergoing haemodialysis it is recommended that dialysis be carried out just prior to the next scheduled dosage since some drug will be removed by dialysis. Where circumstances require an increase in dosage, increases should be made by increasing the frequency of administration of 200 mg doses.

Cimetidine removal by continuous ambulatory peritoneal dialysis is insignificant and there is no need to adjust the conventional renal failure dosage regimen in these patients.

See **Dosage and Administration** for specific recommendations for use in these patients.

Intubated patients receiving mechanical ventilation

Agents that elevate gastric pH may increase the already present risk of nosocomial pneumonia in intubated patients receiving mechanical ventilation in intensive care units.

Cardiovascular

In an intravenous study in dogs, at a dosage level of 25 mg/kg, tachycardia and hypotension were observed. At an oral dose of 336 mg/kg tachycardia was produced. Propranolol prevented or reversed the increase in heart rate.

Impairment of Fertility

Cimetidine exhibited an antiandrogen effect in both rats and dogs. After 12 months dosing in rats at levels of 150 to 950 mg/kg there was a reduction in prostate size in males of all the dosed groups and also a reduction in the size of the testes and seminal vesicles of the top dosed group. Twelve months dosing in dogs at levels of 41 to 504 mg/kg resulted in a reduction in prostate weights. Cimetidine was found to have no significant effect on fertility studies.

Use in Pregnancy (Category B1)

There has been limited experience to date with the use of cimetidine in pregnant patients. No significant adverse effects have been reported. Reproduction studies performed in rats, mice and rabbits have revealed no evidence of impaired fertility or malformation in the foetus due to cimetidine. However, studies in animals and humans have demonstrated that cimetidine crosses the placental barrier and can cross the blood-brain barrier of neonatal animals. Therefore, cimetidine should only be administered to pregnant patients or women of childbearing potential when, in the judgement of the physician, the anticipated benefits outweigh the potential risks.

Use in Lactation

Adequate human data on use in lactation are not available. Cimetidine is excreted in human breast milk and, as a general rule, breastfeeding should not be undertaken while a patient is on the drug.

Use in Children

Clinical experience in children is limited. Therefore, cimetidine therapy cannot be recommended for children unless, in the judgement of the physician, anticipated benefits outweigh the potential risks. In limited experience, 20 to 40 mg/kg/day has been administered in divided doses by mouth or intravenously.

Use in the elderly

It should be borne in mind that some elderly patients may have reduced renal function; however, if renal function is normal, no dosage adjustment is necessary.

Carcinogenicity, Mutagenicity

In a 24 month toxicity study conducted in rats, at dose levels of 150, 378 and 950 mg/kg/day (approximately 4 to 24 times the recommended human dose), a statistically significant higher incidence of benign Leydig cell tumours was seen in the drug treated groups compared to controls. These tumours were present in control groups as well as treated groups and the difference became apparent only in aged rats.

Effects on ability to drive and use machines

Symptoms such as dizziness and drowsiness have been noted in connection with cimetidine. If such symptoms appear, the ability to drive and operate machinery may be impaired.

INTERACTIONS WITH OTHER MEDICINES

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 **Precautions**).

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, quinidine), 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, quinidine, metformin, cyclosporine, tacrolimus 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).

ADVERSE EFFECTS

Adverse events are listed within body systems and categorised by frequency according to the following definitions: common – frequency ≥ 1/100 patients; uncommon – frequency < 1/100 but ≥ 1/1000 patients; rare – frequency < 1/1000 patients.

In a review of patients in short-term clinical trials, cimetidine was found to be well tolerated.

The following adverse effects were observed during the clinical trial programmes:

Body as a whole. ***Common:*** headache

Gastrointestinal. ***Common***: diarrhoea, constipation

Nervous system. ***Common:*** dizziness, drowsiness, tiredness

Dermatological. ***Common****:* rash

Headache and constipation occurred more frequently in placebo treated patients. Overall, the incidence of unwanted adverse effects was comparable between placebo and cimetidine treated groups.

In a review of patients treated with cimetidine in maintenance trials (up to 12 months), the following adverse effects were reported:

Body as a whole. ***Common***: headache; ***Rare:*** fever*, anaphylaxis.

Gastrointestinal. ***Common***: constipation, diarrhoea, vomiting, nausea, flatulence; ***Rare:*** hepatitis*.

Nervous system. ***Uncommon***: depression; ***Common***: tiredness.

Dermatological. ***Common***: rash.

Musculoskeletal. ***Common:*** musculoskeletal pain.

Urogenital. ***Rare:*** interstitial nephritis*.

Metabolic/nutritional. ***Rare:*** pancreatitis*.

Cardiovascular. ***Rare:*** hypersensitivity vasculitis[#], sinus bradycardia, tachycardia, heart block.

Haematologic/lymphatic. ***Rare:*** leucopenia (including agranulocytosis), thrombocytopenia, pancytopenia, aplastic anaemia. A risk /benefit assessment should be made when concomitant use of cimetidine with drugs known to cause bone marrow depression is contemplated.

*cleared on withdrawal of drug

[#]usually cleared on withdrawal of drug

Headache, diarrhoea, dizziness, nausea and vomiting occurred more commonly in placebo treated patients.

Severe skin rash and reversible alopecia have been reported on occasion.

Gynaecomastia and impotence have been reported in some patients receiving high doses. These conditions are usually reversible on discontinuation of cimetidine therapy. The incidence of gynaecomastia and impotence is dependent on dose and duration of treatment. 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 has been reported very rarely.

There have been common reports of myalgia and very rare reports of arthralgia.

Some increases in serum transaminase and small increases in plasma creatinine have been reported and should be borne in mind when treating patients with renal or hepatic insufficiency. The rises in creatinine have occurred in 11% of patients usually during the first week of treatment and have been non-progressive, returning to pretreatment values either during therapy or one week after therapy ceased. The significance of these changes is unknown.

Confusional states, reversible within a few days of withdrawing cimetidine, have been reported rarely, usually in elderly and/or ill patients, such as those with renal insufficiency or organic brain syndrome.

Hallucination has been reported very rarely.

DOSAGE AND ADMINISTRATION

Acute duodenal ulceration:

800 mg at bedtime, or 400 mg morning and at bedtime, or 200 mg three times daily and 400 mg at bedtime.

A single bedtime dose of 800 mg has been shown to be comparable in efficacy to that of a daily dose of 800 mg divided into two administrations (400 mg in the morning and 400 mg at bedtime).

In most cases, healing will occur on this dose within 4 weeks. However, a small number of patients may require an additional period of 2 to 4 weeks therapy. If response is inadequate, the dose may be increased to 400 mg four times a day (with meals and at bedtime).

Maintenance treatment (recurrent duodenal ulceration):

400 mg at bedtime.

Acute gastric ulceration (See **Precautions - Gastric Ulcer**):

800 mg at bedtime, or 400 mg morning and at bedtime, or 200 mg three times daily and 400 mg at bedtime.

In most cases, healing will occur on this dose within 4 weeks. However, a small number of patients may require an additional period of 2 to 4 weeks therapy. If response is inadequate, the dose may be increased to 400 mg four times a day (with meals and at bedtime).

Maintenance treatment (chronic benign gastric ulceration):

400 mg at bedtime for periods of up to one year. In chronic benign gastric ulceration, re-evaluation of the patient should be undertaken at regular intervals.

Zollinger-Ellison syndrome (gastrinoma):

200 mg three times a day and 400 mg at bedtime.

Dosage may be increased, as necessary, to 1.6 to 2 g daily.

Gastro-oesophageal reflux disease:

800 mg at night or in divided doses for up to 12 weeks.

Short-term treatment of heartburn and symptoms of gastro-oesophageal reflux disease:

200 mg up to four times a day for up to 2 weeks. Dosage should not exceed 800 mg per day.

Scleroderma oesophagus:

Usual dose is 1,200 mg daily in divided doses (see **Dosage and Administration** - **Impaired renal function**).

Impaired renal function:

Dosage should be reduced according to creatinine clearance. The following dosages are suggested:

Creatinine clearance (mL/min)	*Dose*
0 - 15	200 mg twice daily
15 - 30	200 mg three times daily
30 - 50	200 mg four times daily
>50	normal dosage

For patients undergoing haemodialysis it is recommended that dialysis be carried out just prior to the next scheduled dosage since some drug will be removed by dialysis. Where circumstances require an increase in dosage, increases should be made by increasing the frequency of administration of 200 mg doses.

Cimetidine removal by continuous ambulatory peritoneal dialysis is insignificant and there is no need to adjust the conventional renal failure dosage regimen in these patients.

Special cases:

In some instances, e.g. draining gastrocutaneous fistula, control of acid secretion may be necessary.

OVERDOSAGE

Symptoms

There have been reports of severe CNS symptoms, e.g. unresponsiveness, following ingestion of cimetidine 20 to 40 g. There have been deaths in adults who were reported to have ingested over 40 g cimetidine orally as a single dose.

In animal toxicity experiments CNS depression, hypotension, tachycardia, liver enzyme elevation and renal abnormalities have been observed.

Treatment

Administer activated charcoal within one hour of ingestion if possible. Institute supportive therapy for the evolving clinical syndrome. Studies in animals indicate that artificial respiration may be of value.

In cases of overdosage, immediately contact the Poisons Information Centre on 131126 (Australia) for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Magicul 200 200 mg tablet: normal convex, pale green film-coated, marked "CE2" on one side, "α" on the reverse; Blister pack* (PVC/PVDC/Al) of 20, 30, 40, 120 and 150's; Bottle* (HDPE and PP cap) of 30, 120 and 150’s

Magicul 800 800 mg tablet: oval, normal convex, pale green film-coated, marked "CE8" on one side, "α" on the reverse; Blister pack* (PVC/PVDC/Al) of 30 and 60's ; Bottle* (HDPE and PP cap) of 30 and 60's.

Store below 30ºC.

Magicul 400 400 mg tablet: White film coated biconvex tablets embossed "CN 400" on one side with "G" on the reverse; Blister pack (PVC/PVDC/Al) of 60's; Bottle* (HDPE and PP cap) of 60's.

Store below 25°C.

*Not marketed.

NAME AND ADDRESS OF THE SPONSOR

Alphapharm Pty Limited

Level 1, The Bond

30-34 Hickson Road

Milliers Point

NSW 2000

ABN 93 002 359 739

www.alphapharm.com.au

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

25 June 2001.

DATE OF MOST RECENT AMENDMENT

14/11/2013

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