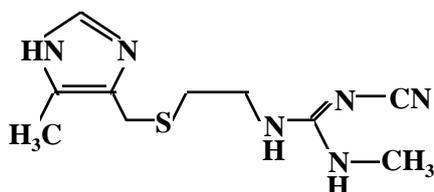


TAGAMET® PRODUCT INFORMATION

(cimetidine)

DESCRIPTION

TAGAMET (cimetidine) is a histamine H₂-receptor antagonist. Chemically it is: 2-cyano-1-methyl-3-{2-(5-methylimidazol-4-yl-methylthio)ethyl} guanidine.



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

PHARMACOLOGY

TAGAMET is a histamine H₂-receptor antagonist and represents a new class of pharmacological agents. It was the first available agent that blocked the action of histamine at the histamine H₂-receptor site of the parietal cells and does so by competitive inhibition.

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

TAGAMET has been shown by *in vitro* studies to be a specific competitive H₂-receptor antagonist without significant interaction at catecholamine, β-receptors, histamine H₁-receptors or muscarinic receptors.

Its potency in terms of administered dose and, more meaningfully, 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 μmol/L is associated with 50% inhibition of maximal acid output.

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

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

Human Pharmacology:

Pharmacokinetic studies carried out in humans have demonstrated that cimetidine is well absorbed orally. Oral absorption studies carried out using a 200mg dose have resulted in blood levels averaging 2.8µmol/L (0.7mg/L) occurring at times ranging from 45 - 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 recovered.

Intravenous infusion of cimetidine labelled with ³H in doses of 75 - 117mg resulted in peak blood concentrations of 2.0 - 4.3 µmol/L (0.5 - 1.1 mg/L). The concentration of cimetidine in the blood declined with a half life of 123 ± 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.

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 200mg dose diminishing after 4 -5 hours and 300mg after 7 - 8 hours, while 400mg 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 5.0 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 - 90% inhibition usually occurred at blood levels above 1.0 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 800mg and 1g 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. TAGAMET 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.

INDICATIONS

1. The short term treatment of proven duodenal ulcer, gastric ulcer.
2. Maintenance treatment in those patients with recurrence of duodenal ulceration after short term therapy.
3. 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.
4. Short term (no more than 12 weeks) treatment of persistent gastro-oesophageal reflux disease.
5. Short term treatment of heartburn (up to 2 weeks) and other symptoms of gastro-oesophageal reflux disease.
6. The treatment of gastrinoma (Zollinger-Ellison Syndrome).
7. Treatment of scleroderma oesophagus.

CONTRAINDICATIONS

Known hypersensitivity to cimetidine.

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 Drugs).

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 H₂ receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk 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.

Coadministration 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 Drugs).

Gastric Ulcer:

Treatment with a histamine H₂-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 TAGAMET is instituted. It is then important to re-endoscope the patient after 8-12 weeks of Tagamet therapy to check that the ulcer has healed.

Gastro-oesophageal reflux disease:

Treatment with TAGAMET for 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).

In patients with impaired renal function or undergoing haemodialysis:

In patients with impaired renal function, 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 200mg 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. It should be borne in mind that some elderly patients may have reduced renal function; if renal function is normal, however, no dosage adjustment is necessary.

In salt restricted diets:

Patients on a low salt diet should be aware that each TAGAMET 800mg effervescent tablet contains 433mg of sodium. The majority of the sodium content is contained in the effervescent mixture.

In intubated patients receiving mechanical ventilation:

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

Cardiovascular:

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

Phenylketonuria:

The TAGAMET 800mg effervescent tablets should be used with caution in persons with phenylketonuria. TAGAMET 800 mg effervescent contains 25mg aspartame per tablet.

Carcinogenicity and Mutagenicity:

In a 24-month toxicity study conducted in rats, at dose levels of 150, 378 and 950mg/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.

Impairment of Fertility:

TAGAMET exhibited an antiandrogen effect in both rats and dogs. After 12 months dosing in rats at levels of 150-950mg/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 41-504mg/kg resulted in a reduction in prostate weights. TAGAMET was found to have no significant effect on fertility studies.

Use in Pregnancy (Risk Category B1):

There has been limited experience to date with the use of TAGAMET 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 fetus due to TAGAMET.

However studies in animals and humans have demonstrated that TAGAMET crosses the placental barrier and can cross the blood brain barrier of neonatal animals.

Therefore, TAGAMET 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 During Lactation:

Adequate human data on use in lactation are not available. TAGAMET passes into 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, TAGAMET therapy cannot be recommended for children unless, in the judgement of the physician, anticipated benefits outweigh the potential risks. In limited experience, 20-40mg/kg per day has been administered in divided doses by mouth or intravenously.

Interactions with Other Drugs:

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 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 sulfonylureas (e.g. glipizide), phenytoin, theophylline, metoprolol, cyclosporine, tacrolimus and diazepam.
- 2) Inhibition of renal tubular secretion via organic cationic 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).

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.

ADVERSE EFFECTS

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

The following adverse events 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 commonly 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 TAGAMET in maintenance trials (up to 12 months) the following side effects were reported most commonly:

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

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

A benefit/risk assessment should be made when concomitant use of cimetidine with drugs known to cause bone marrow depression is contemplated.

§ Cleared on withdrawal of the drug

Usually cleared on withdrawal of the drug

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

Events are listed within body systems and categorised by frequency according to the following definitions: common events reported at a frequency of greater or equal to 1/100 patients; uncommon events reported at a frequency of less than 1/100 but greater or equal to 1/1,000 patients; rare events reported at a frequency of less than 1/1,000 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 TAGAMET therapy. The incidence of gynecomastia 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 (due to inhibition of renal tubular secretion of 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 pre-treatment 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 or ill patients such as those with renal insufficiency or organic brain syndrome. Hallucination has been reported very rarely.

DOSAGE AND ADMINISTRATION

TAGAMET may be administered by mouth.

Acute Duodenal Ulceration

800mg at bedtime

or

400mg morning and at bedtime

or

200mg three times daily and 400mg at bedtime.

A single bedtime dose of 800mg has been shown to be comparable in efficacy to that of a daily dose of 800mg divided into two administrations (400mg in the morning and 400mg 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 2-4 weeks therapy. If response is inadequate, the dose may be increased to 1.6g a day, 400mg four times a day (with meals and at bedtime).

Maintenance Treatment (recurrent duodenal ulceration)

400mg at bedtime.

Acute Gastric Ulceration (see PRECAUTIONS - Gastric Ulcer)

800mg at bedtime

or

400mg morning and at bedtime

or

200mg three times daily and 400mg 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 2-4 weeks therapy. If response is inadequate, the dose may be increased to 400mg four times a day, 1.6 g a day (with meals and at bedtime).

Maintenance Treatment (chronic benign gastric ulceration)

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

Zollinger Ellison Syndrome (Gastrinoma)

200mg three times a day and 400mg at bedtime. Dosage may be increased, as necessary, to 1.6 - 2.0 g a day.

Gastro-oesophageal Reflux Disease

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

Short term treatment of Heartburn and symptoms of Gastro-oesophageal Reflux Disease

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

Scleroderma oesophagus

Usual dose 1200mg daily in divided doses (see dosage in Impaired renal function).

OVERDOSAGE

Clinical Features:

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

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

Management:

Activated charcoal should be given if possible within 1 hour of ingestion.

Institute supportive therapy for the evolving clinical syndrome. Studies in animals indicate that artificial respiration may be of value.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

PRESENTATIONS AND STORAGE CONDITIONS

Tablets 400mg - pale green, capsule-shaped, biconvex, film-coated tablets with "SKF 400" on one side, and "Tagamet" on the other, containing cimetidine base, 400mg, blister packs of 60s. Store below 30°C.

Tablets 200mg - pale green, round, biconvex, film-coated tablets with "SKF 200" imprinted on one side, containing cimetidine base, 200mg, blister packs of 120s. Store below 30°C.

COMPOSITION

Active:

Cimetidine

Inactive:

Tablets 400mg – cellulose-microcrystalline, starch-maize, povidone, sodium lauryl sulfate, magnesium stearate, sodium starch glycolate, indigo carmine CI73015, iron oxide yellow CI77492, Opadry 06H51000 green and carnauba wax.

Tablets 200mg – cellulose-microcrystalline, starch-maize, povidone, sodium lauryl sulfate, magnesium stearate, sodium starch glycolate, indigo carmine CI73015, iron oxide yellow CI77492, Opadry 06H51000 green and carnauba wax.

NAME AND ADDRESS OF THE SPONSOR:

GlaxoSmithKline Australia Pty Ltd
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Boronia Victoria 3155

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