



New Zealand Data Sheet

APO-CIMETIDINE

Cimetidine 200, 400 and 800mg tablets USP

Presentation

APO-CIMETIDINE 200mg tablets are pale green, round, biconvex film coated tablets, identified APO over 200 on one side. Each tablet contains 200mg cimetidine and typically weighs 320mg.

APO-CIMETIDINE 400mg tablets are pale green, oval, biconvex film coated tablets, identified APO-400 on one side. Other side plain. Each tablet contains 400mg cimetidine and typically weighs 640mg.

APO-CIMETIDINE 800mg tablets are pale green, oval, biconvex film coated tablets, identified APO-800 on one side. Other side plain. Each tablet contains 800mg cimetidine and typically weighs 1280mg.

Uses

Actions

Cimetidine is a histamine H₂-receptor antagonist which competitively inhibits the action of histamine on the H₂-receptors of parietal cells. Gastric output is reduced under basal conditions and also when stimulated by food, insulin, betazole, histamine, pentagastrin and caffeine. Pepsin output is indirectly reduced because of the decreased amount of gastric juice.

Cimetidine has been shown to have weak antiandrogenic effects in animal studies (see Adverse Reactions).

Pharmacokinetics

Cimetidine is rapidly and well absorbed after oral administration, with peak plasma concentrations obtained approximately one hour after taking a dose on an empty stomach. Food delays the rate and may slightly decrease the extent of absorption with the peak plasma concentration occurring after 2 hours. Basal gastric acid secretion is inhibited by 80% for 4-5 hours following a single oral dose.

The oral bioavailability is 60-70% due to first-pass metabolism. Cimetidine is partially metabolised in the liver to the sulphoxide and to hydroxymethylcimetidine but most (70%) is excreted by the kidneys unchanged. The elimination half-life is approximately 2 hours in patients with normal renal function; this is prolonged in patients with decreased renal and/or hepatic function and the dosage may need to be adjusted. Cimetidine is about 22% bound to plasma proteins and has an apparent volume of distribution (V_d) of 1.3L/kg.

Indications

Conditions where the reduction of gastric acid secretion is beneficial e.g. treatment of duodenal and benign ulceration, gastro-oesophageal reflux disease, recurrent ulceration of the upper gastrointestinal tract, stomal ulceration, persistent non-ulcer dyspepsia and the short-term treatment of dyspepsia or pain associated with hyperacidity.

Prevention of the recurrence of duodenal or benign gastric ulcers in patients who have a history of recurrence or complications or for whom surgery is contraindicated.

Prevention of stress ulcer in patients at risk of haemorrhage, the management of pathological hypersecretion e.g. Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine

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adenomas and the management of haemorrhage due to peptic ulceration or erosions of the upper gastrointestinal tract.

Reduction of gastric acidity and secretory volume thus reducing the risk of pulmonary damage from aspiration of gastric contents in patients undergoing general anaesthesia.

Cimetidine can be used in conjunction with a H₁ antagonist for the prevention of anaphylactic reaction secondary to histamine release caused by infusion of certain medicines e.g. radio-opaque contrast agents and plasma substitutes.

Dosage and Administration

To prevent any potential interactions, it is advisable that if antacids are also necessary, they should be taken 1 hour before or after cimetidine.

Adults.

Duodenal, Peptic and Benign Gastric Ulcer:

The usual dose is 800mg at night. Reduction of nocturnal gastric acid secretion appears to be the most important factor in healing duodenal ulcers. Alternatively, 400mg may be given twice daily, in the morning and at bedtime.

Patients with an ulcer and who smoke should cease smoking.

Healing will occur in most cases in 4 weeks. To protect against relapse in patients with a tendency of recurrence or complications, therapy may be continued at a reduced dosage of 400mg at bedtime.

Reflux oesophagitis:

In mild to moderate cases, 400mg twice daily or 800mg once daily with the evening meal. More severe cases may require up to 1.6g per day given in 4 divided doses. Cimetidine should be given at mealtimes and at bedtime for up to 12 weeks.

Dyspepsia:

800mg a day in divided doses for 4 to 6 weeks. If there has been no response after this time the patient should be further investigated. For the short term treatment of pain associated with hyper-acidity or dyspepsia 200mg taken as required up to a maximum of 800mg per day.

Zollinger-Ellison Syndrome and other hypersecretory conditions:

Doses need to be individualised and are given in divided doses, with meals and at bedtime. In recent studies median doses of 3-5g daily were required and in patients with gastrinoma doses of up to a maximum of 12g daily have been used for more than a year

Children.

For children aged 1 to 12 years a suggested dose is 20 to 25mg/kg/day in divided doses every 4 to 6 hours.

Less than one year: 20mg/kg/day in divided doses every 4 to 6 hours.

Neonates: 10-15mg/kg/day in divided doses every 4 to 6 hours.

Use in impaired renal function:

Dosage adjustment is only necessary for creatinine clearances of 50mL/min or less. The following dosages are suggested:

Cl_{cr} of 30-50 mL/min, 200mg four times daily; 15-30 mL/min, 200mg three times daily; 0-15 mL/min, 200mg twice daily.

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Use in elderly patients:

If renal and hepatic function is good, dosage reduction may not be necessary. However, most elderly patients show some decrease in the clearance of cimetidine and doses may need to be decreased by 30-50%.

Contraindications

Cimetidine is contraindicated in patients with a known hypersensitivity to the medication.

Warnings and Precautions

Caution is required in patients with impaired kidney and liver function (see Dosage and Administration).

Cimetidine levels are reduced by haemodialysis, but are unchanged by peritoneal dialysis. Therefore cimetidine should be administered after a patient has undergone haemodialysis.

Treatment of gastric ulcers with cimetidine can mask the symptoms associated with carcinoma of the stomach and diagnosis of the condition may be delayed. The delay in diagnosis should be borne in mind in middle aged or older patients with new or recently changed dyspeptic symptoms. If a gastric ulcer is suspected the possibility of malignancy should be eliminated before treatment with cimetidine begins.

Patients should be re-endoscoped 8 to 12 weeks after treatment with cimetidine to check that the ulcer has healed.

Use in Pregnancy

Category B1

Cimetidine crosses the placental barrier and can cross the blood-brain barrier. Animal studies have not indicated any incidence of mutagenicity, carcinogenicity or teratogenicity on the foetus. Cimetidine should be avoided in pregnancy unless the benefits outweigh the potential risk to the foetus. Cimetidine has been used in clinical trials for the prevention of acid aspiration pneumonitis in women undergoing caesarean section or vaginal delivery without harm.

Use in Lactation

Cimetidine passes into human breast milk. Therefore breastfeeding should not be undertaken while a patient is receiving cimetidine.

Adverse Reactions

Apo-Cimetidine is generally well tolerated and adverse effects appear to be reversible on reduction of the dosage or on stopping therapy.

Headache (3.1%), diarrhoea (1.8%), tiredness (1.7%), dizziness (1.3%), drowsiness (1.3%), skin rashes (1.2%) and constipation (1.0%) are the most common side effects.

Reversible alopecia has been reported.

Reversible confusional and other CNS states (e.g. agitation, psychosis, depression, anxiety, disorientation) have been reported especially in the elderly and in patients with renal failure; this is generally resolved by reducing the dose.

Apo-Cimetidine has weak anti-androgenic properties and gynaecomastia has occurred in 0.3-0.4% of patients. Occasionally impotence has been reported with the use of high dosage

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regimens of cimetidine but there is no effect on sperm morphology or motility. These anti-androgenic effects are reversible on withdrawal of therapy.

Less frequently, thrombocytopenia has been associated with the use of H₂-antagonists. Rarely, leucopenia (including agranulocytosis), neutropenia, pancytopenia and a few cases of aplastic anaemia have been reported.

Other adverse effects which occur rarely include allergic reactions, arthralgia and myalgia, interstitial nephritis, hepatotoxicity and pancreatitis. These resolve on withdrawing therapy. Increases in serum transaminases and creatinine, rare cases of hepatitis, fever, interstitial nephritis and pancreatitis may occur during therapy but disappear when treatment is discontinued.

Small increases in plasma creatinine have been reported.

There have been rare occurrences of tachycardia, sinus bradycardia, anaphylaxis and heart block in patients treated with H₂-antagonists.

Interactions

Cimetidine binds to cytochrome P450 and inhibits the breakdown of drugs metabolised by this system. Many interactions have been reported but only a few are of clinical importance.

Toxicity may rarely occur for medicines with a narrow therapeutic index e.g. warfarin-type anticoagulants, phenytoin, theophylline, lignocaine, quinidine, procainamide, flecainide and nifedipine.

With warfarin anticoagulants, close monitoring of the prothrombin time is recommended and adjustment of the anticoagulant dose may be necessary when cimetidine is administered concomitantly.

For the other medicines listed above, plasma levels should be monitored when starting or stopping concomitantly administered cimetidine and dosage adjustments should be made accordingly.

β-blockers, calcium channel blockers, tricyclic antidepressants, benzodiazepines, chlormethiazole and metformin may also be affected by cimetidine. Concomitant use of cimetidine may result in increased blood levels of these medicines. Increased plasma levels of Nifedipine have been reported during concomitant cimetidine use. When concomitant use of nifedipine and cimetidine is deemed necessary cautious titration of nifedipine is advised. Special caution should be exercised in the elderly or those with hepatic or renal disease.

Some antacids reduce the absorption of cimetidine and therefore antacids should be taken at least one hour before or after the administration of cimetidine.

Alteration of gastric pH may affect the absorption of some medicines.

Overdosage

Symptoms:

Animal studies indicate that toxic doses are associated with respiratory failure, CNS depression, hypotension, tachycardia, hepatic enzyme elevation and renal abnormalities.

Doses of up to 20g have resulted in slurred speech, dilated pupils and mental agitation but no significant adverse effects.

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There have been reports of severe CNS symptoms e.g. unresponsiveness, following the ingestion of 20 to 40g of cimetidine.

Deaths in adults have occurred when the reported amount of cimetidine ingested was greater than 40g as a single dose.

Treatment:

Induction of vomiting and/or gastric lavage, clinical monitoring and supportive therapy should be employed. If overdosage produces respiratory failure and tachycardia, management should be with assisted respiration and a beta-adrenergic blocking agent.

Pharmaceutical Precautions

Store at or below 25°C.

Protect from heat, light and moisture. Keep container tightly closed.

Medicine Classification

Prescription only medicine.

Package Quantities

APO-CIMETIDINE 200mg tablets:

Bottles of 100 and 500 tablets.

APO-CIMETIDINE 400mg tablets:

Bottles of 100 and 500 tablets.

APO-CIMETIDINE 800mg tablets:

Bottles of 100 and 250 tablets.

Further Information

Nil

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