PRODUCT MONOGRAPH

MYLAN-CIMETIDINE

(Cimetidine Tablets, USP)

300 mg, 400 mg, 600 mg, 800 mg

Histamine H_2 Receptor Antagonist

Mylan Pharmaceuticals ULC
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Etobicoke, Ontario
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Date of Revision:

PRODUCT MONOGRAPH

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(Cimetidine Tablets, USP)

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PHARMACOLOGICAL CLASSIFICATION

Histamine H_2 Receptor Antagonist

ACTION AND CLINICAL PHARMACOLOGY

Cimetidine, competitively, inhibits the action of histamine on the H_2 receptor of parietal cells, reducing gastric acid output and concentration under basal conditions, and also when stimulated by food, insulin, histamine, pentagastrin, and caffeine. Cimetidine is not an anticholinergic agent.

Cimetidine produces a dose-related reduction in nocturnal acid secretion of 47-83 % over a 6 to 8 hour period or of 54% over a 9 hour period following 400 mg b.i.d. or 300 mg q.i.d., respectively, in patients with duodenal ulcer. Mean acid secretion over a 24-hour period is reduced by about 60% or less following oral dosages of 800 mg daily at bedtime, 400 mg b.i.d., or 300 mg q.i.d. Cimetidine indirectly reduces pepsin secretion by decreasing the volume of gastric juice; however, has no substantial effect on lower esophageal sphincter pressure, gastric motility or emptying, or biliary or pancreatic secretion.

PHARMACOKINETICS

In both healthy individuals and those with peptic ulcer or Zollinger-Ellison syndrome, basal gastric acid secretion is inhibited to a greater extent than is meal-stimulated acid secretion at a given blood concentration of cimetidine.

After oral administration, cimetidine is rapidly and well absorbed with a plasma half life of ~ 2 hrs. An average bioavailability is given between 60-70%, but may be less in elderly

patients with reduced renal or hepatic function. The oral bioavailability of a single 800 mg cimetidine tablet is comparable to that of a single dose of two 400 mg cimetidine tablets. Cimetidine is widely distributed and is 15-25% bound to plasma proteins. Cimetidine crosses the placenta and is distributed into breast milk. Elimination of oral cimetidine is reported as 50% unchanged drug and as 95% total in urine, with traces in feces. Cimetidine is an inhibitor of the metabolism of drugs which are oxydized by the cytochrome P450 system and its effects are dose-dependent. The major metabolite is cimetidine sulfoxide.

INDICATIONS AND CLINICAL USE

MYLAN-CIMETIDINE (Cimetidine tablets) is indicated for conditions where the inhibition of gastric acid secretion is expected to be beneficial, such as: Duodenal ulcer, non-malignant gastric ulcer, gastroesophageal reflux disease, pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and multiple endocrine adenomas.

CONTRAINDICATIONS

MYLAN-CIMETIDINE (Cimetidine tablets) is contraindicated in patients with known hypersensitivity to the drug or any component thereof.

PRECAUTIONS

General:
While laboratory results of cimetidine in the presence of normal alcohol use vary, it is suggested that moderate to heavy use of alcohol concomitant with MYLAN-CIMETIDINE be avoided, and chronic abuse in the presence of MYLAN-CIMETIDINE be regularly monitored.

Use in the Elderly:
No geriatric-specific problems have been documented to date; however, the **CNS** effect of confusion associated with cimetidine is more likely to occur in elderly patients with impaired hepatic or renal function. Reduction in dosage in this group is advised (see **Dosage and Administration**).

Use in Children:
No pediatrics-specific problems have been documented to date.

MYLAN-CIMETIDINE is, however, not recommended for children unless anticipated benefits outweigh potential risks. The reported oral dosage is 20-40mg/Kg/day in divided doses. In the presence of renal or hepatic impairment, however, a reduction in dosage is advised (see **Dosage and Administration**).

Use in Obstetrics:

Pregnancy:
Adequate studies in humans have not been done; however, cimetidine crosses the placenta. Animal studies reveal no impairment of fertility or fetal damage, but do show a weak antiandrogenic effect of cimetidine. MYLAN-CIMETIDINE (Cimetidine tablets) should be used in pregnant women only when the anticipated benefits outweigh the potential risks.

Nursing Mothers:
Since cimetidine is distributed into breast milk, possibly suppressing gastric acidity or inhibiting drug metabolism in the neonate, nursing should generally not be undertaken during treatment with MYLAN-CIMETIDINE.

Patients with Special Diseases and Conditions:

Hemodialysis is considered an ineffective means of decreasing the total body load of cimetidine and its metabolites. Cimetidine should, however, be administered at the end of dialysis and every 12 hours during the interdialysis period. **Ambulatory peritoneal dialysis** does not require adjustment of the conventional renal failure cimetidine dosing regimen. **Severely impaired renal function** patients show a significantly lower nonrenal clearance than patients with normal renal function, suggesting that cimetidine metabolism may be impaired in uremic patients, necessitating dosage reduction.

Liver cirrhosis including Laennec's cirrhosis does not appear to alter the pharmacokinetics of cimetidine. The clearance of cimetidine appears to be predictable from creatinine clearance and prothrombin time in such patients. Since the blood-brain barrier permeability of cimetidine appears to be increased in patients with cirrhosis, resulting in an increased CNS plasma concentration ratio, and since decreased hepatic elimination of cimetidine appears possible due to decreased hepatic blood flow after cimetidine therapy, close monitoring of the cirrhotic patient is advisable. Dosage reduction may be necessary.

Burn patients show increased cimetidine clearance; thus explaining the decreased effectiveness of this drug in those patients. Dose schedules may need to be altered to compensate for the enhanced clearance of this drug.

Drug Interaction. Cimetidine inhibits hepatic cytochrome P-450 and P-448 mixed function oxidase, may reduce hepatic blood flow, and reduces gastric pH. Dosage of drugs metabolized by microsomal enzyme systems or those with high hepatic extraction ratios may require adjustment when concomitant cimetidine treatment is

initiated or discontinued; especially, drugs with low therapeutic ratios or in patients with renal and/or hepatic impairment. While study results are controversial, alcohol should be avoided when administering MYLAN-CIMETIDINE (cimetidine tablets). To prevent decreases in cimetidine bioavailability, antacids should be given 1/2 - 1 hour prior to, or after MYLAN-CIMETIDINE (Cimetidine tablets) administration.

Anticoagulants (e.g. Warfarin) present a major interaction due to increased blood concentration of **warfarin** possibly potentiating bleeding. If the concomitant use of Warfarin and cimetidine can not be avoided, careful attention must be directed towards adjusting the Warfarin dosage accordingly.

Tricyclic antidepressants interact with cimetidine through increase in tricyclic serum concentrations, possibly requiring drug substitution. Interaction with **theophylline** leads to increased theophylline concentrations (toxicity) necessitating a 20-40% re reduction in theophylline dose.

Metoprolol and propranolol interaction with cimetidine increases by up to 2-fold their concentration, possibly causing bradycardia and hypotension. **Glibenclamide (glyburide)** causes a decrease in clearance of sulphonylureas, possibly leading to hypoglycemia. Cimetidine should be given at least 2 hours after ketoconazole to avoid reduction in ketoconazole absorption. Cimetidine interaction enhances the actions of **nifedipine,** leading to hypotension, tachycardia. Administer cimetidine at least 2 hours after **sucralfate** to avoid a decrease in sucralfate effectiveness.

Cimetidine interaction with **oxidation-metabolized benzodiazepines (e.g. diazepam, chlordiazepoxide)** results in increased serum concentrations of named benzo diazepines and exaggerated effects including sedation.

Since monitoring the use of benzodiazepines in the elderly is a normal precaution, it is prudent to take additional precautions when concomitant cimetidine is being administered.

Cimetidine interactions in patients using e.g. **phenytoin, carbamazepine, valproic acid, lidocaine, quinidine, metronidazole, procainamide or triamterene** may lead to decreased hepatic metabolism and subsequently to an increase in side effects. **Laboratory Tests:** Cimetidine may inhibit the cutaneous histamine response, leading to false-negative skin test results. Serum concentrations of creatinine and transaminase may be increased during cimetidine treatment.

Information to be provided to the Patient: We advise that the physician, in addition to Information for the Consumer, provide consultation as per monograph section on PRECAUTIONS, specific to the patient's profile. Included should be the possible avoidance of certain foods, drinks, alcohol, and smoking.

ADVERSE REACTIONS

General: A prospective survey of 9907 patients treated with cimetidine produced 577 adverse reactions in 442 patients. The most frequent reactions involved the gastrointestinal (2.1%) and the central nervous system (1.2%). The frequency of severe adverse effects is low. Risk factors for adverse drug reactions include multiple medical illnesses, hepatic or renal dysfunction, and the elderly combined with these risk factors.

Central Nervous System: Neurological dysfunction may be caused by toxic concentration of cimetidine sulphoxide, a major metabolite of cimetidine. Predisposing factors for the development of cimetidine-induced confusion include: high doses of cimetidine, older age, pre-existing psychiatric illness, poor renal function, cerebral impairment, and simultaneous treatment with psychotropic medications. Confusion, reported as rare to 1 % occurrence, is reversible upon discontinuation of cimetidine, with symptoms usually resolving within 12 to 48 hours. This side effect may mimic an alcohol withdrawal syndrome (delirium tremens). Cimetidine therapy has also been associated with dizziness (2%), drowsiness (2%), headaches (3-4%), somnolence. restlessness, lethargy, agitation. visual hallucinations, seizures, and slurred speech. These side effects are primarily reported in the elderly on high dose cimetidine, and in patients with renal and/or hepatic impairment. Other reported nervous system associated cimetidine side effects are increased sweating, dry mouth. ringing or buzzing in the ears, fatigue. and possibly cimetidine-induced fever. These adverse events are reported as rare to less than 1 %.

Gastrointestinal System: 1-2% occurrence of cimetidine-induced nausea/vomiting and mild transient diarrhea has been reported. Perforation of duodenal, esophageal and gastric ulcers has been reported following abrupt discontinuation of cimetidine treatment. Pancreatitis, which subsided following discontinuance of the drug, had been reported. Rare cases of hepatitis with or without jaundice have been reported in patients following the administration of histamine H2-receptor antagonists; however, a direct relationship had not been established, and the condition reacts favorably to withdrawal of cimetidine. Except for mild increases in AST(SGOT) and ALTISGPT) concentrations, cimetidine-associated hepatic toxicity is rare.

Urogenital System: Small increases in plasma creatinine are not progressive and tend to disappear towards the end of therapy. A rare cimetidine-associated acute interstitial nephritis (biopsy) with fever, malaise, mild eosinophilia, and evidence of decreased renal function appears to be a hypersensitivity reaction, with prompt improvement upon cimetidine withdrawal. Mild bilateral gynecomastia, and breast soreness in both men and women were reported after 1 month of treatment; however, no evidence of endocrine dysfunction was found. Gynecomastia may be related to the weak antiandrogenic effect of cimetidine. Rare to 1 % occurrence was reported for decreased libido or impotence.

Haematology: Cases of thrombocvtopenia and aplastic anemia were reported. Agranulocytosis, neutropenia and other blood dyscrasias are more likely to occur in patients with serious concomitant illnesses or various oncology treatments. With appropriate monitoring, these conditions are reversible.

Dermatology: Various forms of rashes and urticaria have been reported. Allergic reactions (hypersensitivity, anaphylaxis, vasculitis) are rare with cimetidine treatment. Sporadic reports of severe generalized dermatological reactions such as Stevens Johnson syndrome, epidermal necrolysis, erythema multiforme, or exfoliative erythroderma could be found in patients receiving cimetidine therapy.

Cardiovascular System: Monitoring the cardiac patient on cimetidine treatment is necessary to prevent a rare tachycardia.

Other Body Systems: Reversible alopecia as well as reversible arthralgia and myalgia have been reported. There are reports of joint or muscle pain, and exacerbation of joint symptoms in patients with preexisting arthritis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Patients, especially the elderly and those with impaired renal and/or hepatic impairment, being administered long-term high-dose, or experimentally excessive dose of cimetidine, must be monitored for severity of symptoms indicating overdosage parameters, to, immediately, start controlled withdrawal of cimetidine. The following are 2 cases of recovery after cimetidine overdosage:

A 25-year old man, after taking 12g of cimetidine, presented disorientation and nonsensical speech. He recovered fully after 24 hours.

A 35-year old man, after taking one hundred and twenty 200 mg cimetidine tablets concomitant with 400 mg oxazepam, was unconscious for 6 hours. He responded favourably to forced diuresis.

Treatment: Since oral cimetidine overdosage may produce seizures as well as cardiovascular emergencies, and since no specific antidote for overdose with histamine H_2-receptor antagonists is available, treatment should be symptomatic and supportive, additionally suggesting the following:

Induction of emesis and/or use of gastric lavage.
Intravenous diazepam for seizures,
Atropine for bradycardia,
Lidocaine for ventricular arrhythmias, and
Continuous laboratory monitoring.

DOSAGE AND ADMINISTRATION

Guide to cimetidine dose in patients with renal failure

Creatinine clearance (mL/min)	**Dose (mg)**
>30	800/day
15-30	600/day
5-14	400/day

5-15

Guide to cimetidine dose per age group of patients

Children (3-16 years) Benefit/Risk		15-20 mg/Kg/day
Elderly (65 years)	65-75	600 mg/day
	76-84	400 mg/day
	85	200 mg/day

The presence of renal and/or hepatic impairment in the dose per age group must lead to further reduction in dose.

Use of antacids for pain relief should be scheduled 1/2 - 1 hour prior to, or after MYLAN-CIMETIDINE (Cimetidine tablets), to avoid decreased absorption of cimetidine. Avoidance of alcoholic beverages should be instructed during administration of MYLAN-CIMETIDINE (Cimetidine tablets).

Duodenal Ulcer:
Currently, for the treatment of active duodenal ulcer, the MYLAN-CIMETIDINE 800 mg bedtime regimen is considered the adult dosage of choice. Other adult dosage regimen are: 300 mg four times a day, with meals and at bedtime. 400 or 600 mg twice a day, at breakfast and at bedtime. 200 mg 3 times daily with an additional 400 mg dose at bedtime. A daily dose should not usually exceed 2400 mg per day in divided doses. Although, healing may occur within the first two weeks of treatment in some patients and within four weeks in others, treatment should usually be continued for 4 to 6 weeks, or, until endoscopic healing is obtained. Use of cimetidine at full therapeutic dosage for periods longer than 6-8 weeks is rarely needed for healing duodenal ulcers. A 1600 mg daily bedtime dose of cimetidine in some heavy smoking patients with endoscopically demonstrated duodenal ulcers (>1cm) has been found to produce a more rapid healing in some ulcer patients.

Maintenance: Treatment of recurrent duodenal ulcer: 300 mg MYLAN-CIMETIDINE b.i.d. or 400 mg MYLAN-CIMETIDINE once daily at bedtime for 6 to 12 months. There are reports that patients have been maintained on 400 mg cimetidine at bedtime for periods of up to five years.

Gastric Ulcer:
Cimetidine therapy must not be instituted unless radiologic and endoscopic evaluation demonstrates the gastric ulcer to be benign. Currently, for the treatment of active, benign gastric ulcer, the

800 mg MYLAN-CIMETIDINE bedtime regimen is preferred for most patients because of maximal patient compliance and decreased drug interactions. Other adult dosage regimen are: 300 mg four times daily, with meals and at bedtime. 600 mg b.i.d. at breakfast and bedtime. A daily dose should not usually exceed 2400 mg in divided doses. Although, healing may occur within the first 2-4 weeks in some patients, treatment should continue from 4-6 weeks, or, until endoscopic healing is demonstrated. Efficacy beyond 8 weeks treatment for gastric ulcer has not been established. In a patient in whom a gastric ulcer persists past 8-12 weeks of cimetidine treatment or reappears soon after therapy is discontinued, gastric cancer should be suspected.

A **Benefit/Risk** pediatric dose of 20-40 mg/Kg/day may be utilized in divided doses for acute cases of duodenal or gastric ulcer. Renal and/or hepatic impairment in this group requires appropriate reduction in cimetidine dose.

It is strongly advised to monitor patients on long-term full or high dose cimetidine therapy, to prevent symptoms of overdosage.

Gastric Hypersecretory Conditions (e.g: Zollinger-Ellison syndrome, systemic mastocytosis, multiple endocrine adenomas): The usual adult oral treatment dose is 300 mg 4 times daily, with meals and at bedtime. A larger than usual dosage may be required in some patients, but should not usually exceed 2400 mg per day. Increases in dosage should be made by augmenting the frequency of administration. Therapy should be continued for as long as clinically indicated.

Gastroesophageal Reflux: For symptomatic relief, the usual adult oral cimetidine dose ranges from the lower 300 mg 4 times daily, with meals and at bedtime regimen to 400 mg 4 times daily, with meals and at bedtime, or 800 mg twice daily in the morning and at bedtime. Treatment dosage and duration for adults are reported as 800 mg to 1600 mg daily for 8-12 weeks.

CAUTION: 40-80 mg/Kg/day cimetidine, divided into 4 or more doses as **Benefit/Risk** pediatric dose, may be utilized for acute cases of Gastroesophageal Reflux. Concomitant renal and /or hepatic impairment require appropriate dose adjustment.

NSAID-induced gastric ulcers: Clinical Practice Guideline suggest, to stop the NSAID whenever possible. During the treatment period, an appropriate pain relief substitute should be considered. Patients at high risk in this group should be considered for Misoprostol therapy at 1200 μg orally 4 times/day.

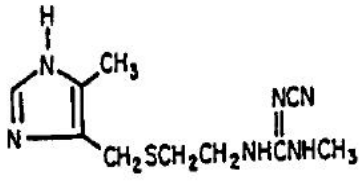
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Cimetidine USP

Chemical Name: Guanidine,N"-cyano-N-methyl-N"-[2-[[(5-methyl-1H-imidazol-4-yl)methyl]thio]ethyl]-

Structural Formula:



Molecular Formula: $C_{10}H_{16}N_6S$

Molecular Weight: 252.35

Physical Properties: White to off-white crystalline powder; odourless to slight mercaptan odour.

Solubility: Soluble in alcohol and in polyethylene glycol 400. Freely soluble in methanol. Sparingly soluble in isopropyl alcohol. Slightly soluble in water and in chloroform. Practically insoluble in ether.

pKa: 7.09

pH: Only slightly soluble in water.

Melting Range: 139° – 144°C

COMPOSITION: Cimetidine Tablets, USP

Non-medicinal ingredients: Corn Starch, MagnesiumStearate, Microcrystalline Cellulose, Povidone, Sodium Starch Glycolate for 200,300,400 & 600 mg

Magnesium Stearate, Sodium Starch Glycolate, Povidone for 800 mg

Tablets	
300 mg	Opadry II Green (Y-22-11031-A)
400 mg	Opadry II Green (Y-22-11031-A)
600 mg	Opadry II Green (Y-22-11031-A)
800 mg	OpaSpray K-1-2302 Orange, Hydroxypropyl Methylcellulose, Hydroxypropyl Cellulose, Polyethylene Glycol.

Stability and Storage Recommendations: Store at room temperature (15°C – 30°C) in tight, light-resistant container.

AVAILABILITY OF DOSAGE FORMS:

300 mg	Round, biconvex, light green film-coated tablets; G on one side, CM on the other. 300
400 mg	Ellipsoid, biconvex, light green film-coated tablets; G on one side, CM 400 on the other.
600 mg	Ellipsoid, biconvex, light green film-coated tablets; G on one side, CM 600 on the other.
800 mg	Ellipsoid, biconvex, peach film-coated tablets with bevelled edges; G on one side, CM 800 on the other.

MYLAN-CIMETIDINE tablets are alcohol-, gluten-, tartrazine-, sucrose-, sulfite- and lactose-free.

MYLAN-CIMETIDINE 800mg tablets are sodium-free. The other dosage forms contain < 1mmol (< 1mg) sodium.

ENERGY: 300 mg tablets =0.4 kj(0.1 kcal),
400 mg tablet = 0.8 kj(0.2 kcal),
600 mg tablet = 1.2 kj(0.3 kcal),
800 mg tablet = 2.9 kj(0.7 kcal).

INFORMATION FOR THE CONSUMER
PrMYLAN-CIMETIDINE
(Cimetidine Tablets)

AVAILABILITY OF DOSAGE FORMS:

300 mg	Round, biconvex, light green film-coated tablets; G on one side, CM on the other. 300
400 mg	Ellipsoid, biconvex, light green film-coated tablets; G on one side, CM 400 on the other.
600 mg	Ellipsoid, biconvex, light green film-coated tablets; G on one side, CM 600 on the other.
800 mg	Ellipsoid, biconvex, peach film-coated tablets with bevelled edges; G on one side, CM 800 on the other.

MYLAN-CIMETIDINE (CIMETIDINE) IS AVAILABLE ON PRESCRIPTION ONLY

ACTION: MYLAN-CIMETIDINE (Cimetidine) is a histamine H_2-receptor antagonist or H_2-blocker. It decreases the amount of stomach acid and indirectly the amount of pepsin. This action is necessary to treat and prevent acid-pepsin disorders of the gastrointestinal system.

USES: MYLAN-CIMETIDINE (Cimetidine) is used to treat and prevent the following:
Duodenal ulcer
Non-malignant gastric ulcer
Gastroesophageal reflux disease
Zollinger Ellison syndrome (Hypersecretory disorder)

The use of MYLAN-CIMETIDINE (Cimetidine) for other gastrointestinal disorders must also depend upon the diagnosis of your doctor.

Maintenance is the therapy to prevent recurrence (relapse) of ulcers.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN

DOSAGE AND ADMINISTRATION
Use of antacids for pain relief should be scheduled 1/2 - 1 hour prior to, or after MYLAN-CIMETIDINE (Cimetidine), to avoid decreased absorption of cimetidine.

Alcoholic beverages and heavy smoking should be avoided during administration of MYLAN-CIMETIDINE (Cimetidine).

DUODENAL AND GASTRIC ULCER

- 800 mg at bedtime
- 300 mg four times a day, with meals and at bedtime
- 400 or 600 mg twice a day, at breakfast and at bedtime
- 200 mg three times daily with meals, plus an additional 400 mg dose at bedtime
- A daily dose should not exceed 2400 mg in divided doses

Children and the Elderly: As directed by your doctor.

Maintenance Therapy: Duodenal Ulcer
Adults: 300 mg two times a day, at breakfast and at bedtime, or 400 mg only at bedtime, or as directed by your doctor
Children and the Elderly: As directed by your doctor

Take MYLAN-CIMETIDINE (Cimetidine) as directed by your doctor for the full time prescribed, even if you begin to feel better.

GASTROESOPHAGEAL REFLUX As directed by the doctor

- 300 mg four times a day, with meals and at bedtime
- 400 mg four times a day, with meals and at bedtime
- 800 mg twice daily at breakfast and at bedtime
- Usual treatment lasts from 8 to 12 weeks

ZOLLINGER ELLISON SYNDROME **As directed by the doctor**

CONTRAINDICATIONS: Hypersensitivity to cimetidine, ranitidine, famotidine or nizatedine, or components thereof.
Inform your doctor, if you have ever had any unusual or allergic reaction to the above drugs.

PRECAUTIONS: **Consult your physician, nurse or pharmacist,** if you are taking, or intend to take any prescription and/or non-prescription drugs, as well, if you are allergic to certain foods or preservatives. Since many drugs, including alcohol interact with cimetidine and cause side effects, it is prudent to avoid these drugs during treatment with MYLAN-CIMETIDINE (Cimetidine). **Inform your physician,** if you have or recently had a medical problem, such as kidney and/or liver disease.

Elderly/Children: As directed by your doctor, dosage must be carefully controlled. Elderly patients may experience confusion and dizziness.

Pregnancy: Adequate studies in humans have not been done; therefore, **inform your physician,** if you are pregnant, or intend to become pregnant. MYLAN-CIMETIDINE (Cimetidine) should be used in pregnant women only, when the anticipated benefits outweigh the potential risks.

Nursing Mothers: Since cimetidine is distributed into breast milk, nursing should not be undertaken, unless discussed with your doctor.

SIDE EFFECTS: The frequency of severe side effects is low. Risk factors for side effect reactions include multiple medical illness, hepatic and/or renal dysfunction, drug interactions with MYLAN-CIMETIDINE (Cimetidine), and the elderly combined with these risk factors. Reversible mild to bothersome side effects are: Headaches, dizziness, drowsiness, increased sweating, dry mouth, ringing or buzzing in the ears, fatigue, confusion, nausea/vomiting, diarrhea, joint or muscle pain, decreased sexual desire (at high dose), swelling of breasts or soreness of breasts in females and males, and skin rash. Reversible hair loss has been reported. Most side effects may disappear during treatment. Severe rashes, heart irregularities and fever should be reported to your doctor; they are reversible upon reduction of medication. Any unusual manifestation or side effect

upon treatment with MYLAN-CIMETIDINE (Cimetidine) report to your doctor, nurse, or pharmacist.

STORAGE: Store at room temperature (15°C-30°C) in tight, light-resistant containers.

SAFELY DISCARD OUTDATED MEDICATION AND MEDICATION NO LONGER REQUIRED

PRECLINICAL PHARMACOLOGY

PHARMACODYNAMICS

In vitro and in vivo, oral or intravenous cimetidine acts as a competitive inhibitor of histamine H_2-receptor antagonists. Both oral and intravenous cimetidine inhibits basal (non-stimulated) acid secretion and that stimulated by histamine or pentagastrin, but is generally much less effective in inhibiting carbachol-stimulated acid secretion.

Controlled experimental studies have shown that pretreatment with cimetidine protects rats against gastric ulceration caused by stress, pyloric ligation and treatment with aspirin, or indomethacin, and duodenal ulcers induced by carbachol-histamine. Cimetidine also protected guinea pigs against histamine-induced ulceration. Cimetidine does not prevent gastric ulcers produced by serotonin or reserpine in rats. Oral cimetidine given for 10-12 consecutive days accelerated the spontaneous healing of gastric and duodenal ulcers produced by acetic acid in rats.

Cimetidine was given to a Haidenhain pouch-fitted conscious dog as powder in a hard gelatin capsule. A dose of 20 gmoles/Kg gave a mean inhibition of 90% on maximal histamine-stimulated gastric acid secretion. Peak effect was measured at between 1.25 and 1.50 hours after administration. An oral dose of 100 μmoles/Kg was necessary in the 24-hour starved rat, to almost completely abolish basal gastric acid secretion.

Oral treatment with 450 mg/dog/day cimetidine in three divided doses for 14 days, produced acceleration of healing of duodenal acetic acid ulcers, but showed little influence on gastric ulcers.

Large doses of cimetidine significantly inhibit edema formation in thermally injured rat skeletal muscle. The minimal effective dose up to 4 hours after injury was between 0.1 to 0.2 mg/g body weight.

PHARMACOKINETICS

In rats and dogs, cimetidine is rapidly **absorbed** with the plasma half-life being about 1 hour.

Cimetidine is widely **distributed** throughout all tissues except the brain and thyroid, from which, with the exception of the liver, kidney and adrenal cortex, it is rapidly eliminated. **Plasma binding,** since lower than 85% in rat, dog and man, does probably not affect the duration of cimetidine in the circulation.

Species	Plasma C-Cimetidine Concentration	% Plasma Binding
Rat	0.5 – 50 μM	**9.6% - 23.3%**
Dog	0.5 - 50 μM	**6.7% - 23.8%**
Man	0.2-200 μM	**18.0%- 26.3%**

The dog and rat are appropriate models to investigate the passive diffusion and removal of cimetidine into the cerebrospinal fluid.

Elimination and Metabolism: When C-cimetidine was given orally to male rats, 58% of the dose (30 mg/Kg) was excreted in 24-hour urine, with ~ 50% being cimetidine. In the 24-hour urine of female rats, 74% of radioactivity represented unchanged cimetidine. In dogs after oral (30 mg/Kg) cimetidine, 81 % of 24-hour urinary radioactivity was excreted, with ~ 75% being cimetidine. The following demonstrates urinary and fecal excretion in dogs after oral 30 mg/Kg (2.21 μCi/Kg) and intravenous 30 mg/Kg (0.82 μCi/Kg) cimetidine:

TIME (Hr)	RADIOACTIVITY RECOVERED Oral (% or dose)	Intravenous (% of dose)
Urine: 0-24	**80.6 ± 4.33**	**84.2 ± 4.36**
24-48	**9.9 ± 1.85**	**8.3 ± 3.53**
48-72	**1.4 ± 0.3**	**0.8 ± 0.43**
Total	**91.9 ± 2.19**	**93.3 ± 2.95**
Feces: 0-24	**------**	**0.9 ± 0.48**
24-48	**3.4 ± 0.76**	**1.1 ± 0.76**
48-72	**2.1 ± 1.5**	**1.0 ± 0.52**
72-96	**0.8 ± 0.60**	**0.7 ± 0.33**
Total	**6.3 ± 1.23**	**3.7 ± 1.07**
TOTAL RECOVERY:	**98.2 ± 1.45**	**97.0 ± 2.22**

Sulfoxide is the major metabolite in rats, dogs and man.

TOXICOLOGY

Acute Toxicity:

In dogs, the LD_{50} value of cimetidine after oral dosing with solution was ~ 2600 mg/Kg. Death occurred within 4 hours of dosing and was preceded by clonic convulsions, indicating a possible penetration into the CNS at high dose levels. The animals which died had peak blood levels of cimetidine in excess of 770 gM. The following LD_{50} values, using cimetidine as solution, involved groups of 10 animals/sex/species.

SPECIES	ROUTE	LD_{50}(mg/Kg)
Mouse	i v	150
Mouse	ip	470
Mouse	po	2600
Rat	iv	106
Rat	ip	650
Rat	po	5000
Hamster	ip	880
Hamster	po	4000

All deaths occurred within 24 hours after dosing, but usually within the first 2 hours. No significant difference in toxicity between sexes was observed.

Chronic Toxicity:

Repeated oral cimetidine dose studies in rats.

950 mg/Kg (680 times the estimated intraduodenal ID_{50} for inhibition of stimulated gastric acid secretion in the anesthetized rat)

30-day: Excessive salivation, slight increase in liver weights, slightly low hemoglobin in females.

90-day: Excessive salivation, perinea! soiling, slight increase in liver weights.

6-month: Excessive salivation, perineal soiling, increase in liver weights, prostates and seminal vesicles lighter than controls.

12-month: Excessive salivation, perineal soiling, increase in liver weights, prostates and seminal vesicles lighter than controls.

24-month: Excessive salivation, perineal soiling, increase in liver weights, prostates and seminal vesicles lighter than controls.

378 mg/Kg 30-day: Slightly low hemoglobin in females.

90-day: No results reported.

6-month: Increased liver weights in males. Seminal vesicles lighter than controls.

12-month: Prostates slightly lighter than controls.

24-month: Prostates and seminal vesicles lighter than controls.

Repeated oral cimetidine dose studies in dogs.

504 mg/Kg (203 times the estimated ID_{50} for inhibiting of maximally stimulated gastric acid secretion).

	3-month:	No results reported.
	6-month:	Transient tachycardia and rapid weight loss (early weeks). Slight liver damage. Small prostates. One dog killed (liver and kidney damage).
	12-month:	Transient tachycardia and rapid weight loss (early weeks). No liver damage. One dog killed (liver and kidney damage).
336 mg/Kg	**3-month:**	Transient tachycardia and slight weight loss (early weeks). Small prostate.
	6-month:	Transient tachycardia. Small prostates.
	12-month:	Transient tachycardia. Small prostates.

The **144 mg/Kg** dose in dogs showed small prostates at **6-month** and **12-month** duration. The **41 mg/Kg** dose at **6-month** duration showed small prostates. Haematology and histopathology, including the gut, were normal.

CARCINOGENICITY/MUTAGENICITY

In a 24-month toxicity study, conducted in rats at dose levels of 150, 378, and 950 mg/Kg/day, a small increase in the incidence of benign Leydig cell tumors in each dosage group was observed. These tumors were common in controls as well as treated groups. The difference became apparent only in aged rats.

No cases of mutagenicity due to cimetidine in laboratory animals were reported.

REPRODUCTION/TERATOLOGY

In a male fertility study in which rats were dosed orally with 950 mg/Kg daily cimetidine for 70 days prior to mating, no effects on mating performance or fertility were observed.

During oral doses of up to 950 mg/Kg cimetidine to pregnant rats, rabbits, and mice, only in the treated rats were a few more embryos lost between ovulation and implantation than in controls.

Teratological studies have been completed in the rat, rabbit, and mouse, all at oral doses up to 950 mg/Kg cimetidine daily. No significant adverse effects were observed.

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