PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] CIMETIDINE

Cimetidine

Tablet, 200, 300, 400, 600 and 800 mg, oral

USP

ATC Code: A02BA01

Histamine H_2 - Antagonist

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Date of Initial Authorization:
DEC 31, 1982

Date of Revision:
FEB 10, 2022

Submission Control Number: 256184

RECENT MAJOR LABEL CHANGES

1 Indications, 1.2 Geriatrics	02/2022
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	02/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CIMETIDINE (Cimetidine) is primary therapy - for conditions where the inhibition of gastric acid secretion is likely to be beneficial such as:

- Duodenal ulcer therapy.
- Non-malignant gastric ulcer therapy.
- Prophylaxis of recurrent duodenal or gastric ulcer.
- Gastroesophageal reflux disease.
- Pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and multiple endocrine adenomas.
- Treatment of NSAID-induced lesions (ulcers, erosions) and gastrointestinal symptoms and prevention of their recurrence.
- Adjunctive therapy in the management of cystic fibrosis in children.

1.1 Pediatrics

Pediatrics (16 to 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of cimetidine in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use. See 1 INDICATIONS, 4.2 Recommended Dose and Dosage Adjustment, and 8.1 Adverse Reaction Overview.

1.2 Geriatrics

Geriatrics (>65 years of age): No data are available to Health Canada; however, evidence suggests that use in the geriatric population is associated with differences in safety. See 7 WARNINGS AND PRECAUTIONS, Gastrointestinal and 8.1 Adverse Reactions Overview, CNS.

2 CONTRAINDICATIONS

CIMETIDINE is contraindicated in:

- Patients who are hypersensitive to the drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing considerations

- Dosage adjustment for patients with impaired renal function: Patients with severely impaired renal function have been treated with cimetidine; however, such usage has been very limited. On the basis of this experience, the recommended dosage is 300 mg every 12 hours orally. Should the patient's condition require, the frequency of dosing may be increased to every 8 hours or even further with caution. In severe renal failure accumulation may occur and the lowest frequency of dosing compatible with an adequate

patient response should be used. When liver impairment is also present, further reductions in dosage may be necessary.

- Hemodialysis: Hemodialysis reduces the level of circulating cimetidine. Greater than 80% of a 300 mg intravenous dose is cleared in a single 4 hour period of hemodialysis. It is completely cleared in an 8 hour period. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose is administered after dialysis treatment.
- Peritoneal Dialysis: Peritoneal dialysis does not appear to remove cimetidine to any appreciable extent.

4.2 Recommended Dose and Dosage Adjustment

In clinical studies, cimetidine has been used in divided doses of up to 2400 mg/day in adults.

Duodenal Ulcer and Non-Malignant Gastric Ulcer:

- For active ulcer: The recommended adult oral dose is 800 to 1200 mg per day. This may be given as follows: 800 mg once daily at bedtime; or 600 mg twice daily, at breakfast and bedtime; or 300 mg four times daily with meals and at bedtime.
- In some patients, 400 mg twice daily has been shown to be effective.
- While healing with cimetidine may occur during the first week or two, treatment should be continued for at least four weeks for duodenal ulcer and at least six weeks for non-malignant gastric ulcer unless healing has been demonstrated by endoscopic examination.
- While some patients may require concomitant antacids initially, cimetidine alone has been shown to promote rapid relief of symptoms.

Prophylaxis of Recurrent Duodenal or Gastric Ulcer:

- For most adult patients the following regimens have been shown to be effective: 400 mg once daily at bedtime; or 300 mg twice daily, at breakfast and bedtime.
- Daily maintenance therapy may be used for those patients who would benefit from a reduction of gastric acid secretion, as well as those patients who are known to suffer frequent recurrence of duodenal or gastric ulcers, and should be continued for at least 6 to 12 months. Re-evaluation of the gastric ulcer patient should be undertaken at regular time intervals.

Gastroesophageal Reflux Disease (GERD):

- The recommended adult oral dose for gastroesophageal reflux disease is 1.2 g per day which may be given as follows: 800 mg once daily at bedtime; or 600 mg twice daily, at breakfast and at bedtime; or 300 mg four times daily with meals and at bedtime, for 8 to 12 weeks.
- While some patients may require concomitant antacids initially, cimetidine alone has been shown to promote rapid relief of symptoms.

Pathological Hypersecretion Conditions (e.g., Zollinger-Ellison Syndrome, systemic mastocytosis and multiple endocrine adenomas):

- The recommended adult dosage is 300 mg four times a day, with meals and at bedtime. In some patients, it may be necessary to administer higher and/or more frequent doses to control symptoms. Dosage should be adjusted to individual patient's needs, but usually should not exceed 2400 mg per day.

Adjunctive therapy in the management of cystic fibrosis in children:

- Clinical experience in pediatric patients is limited; however, doses of 20 to 40 mg/kg per day have been used.

NSAID-Induced Lesions (ulcers, erosions) and Gastrointestinal Symptoms:

- The recommended adult dose of cimetidine is 800 mg/day, either as 800 mg at bedtime or 400 mg twice daily, for 8 weeks.
- In patients with NSAID-induced lesions who have responded to an initial course of treatment and who require ongoing NSAID therapy, recurrence of lesions may be prevented by continual concomitant maintenance treatment with cimetidine. The recommended dosage for maintenance treatment is 400 mg of cimetidine at bedtime.

4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the regular dosing schedule.

5 OVERDOSAGE

- In cases reported to date, involving oral ingestion of up to 20 grams of cimetidine, transient adverse effects similar to those encountered in normal clinical experience were noted and recovery has been uneventful.
- There have been reports of severe CNS symptoms, including unresponsiveness, following ingestion of between 20 and 40 mg of Cimetidine, and extremely rare reports following concomitant use of multiple CNS-active medictions and ingestion of Cimetidine at doses less than 20 mg.
- Two deaths were reported in adults who ingested over 40 mg orally on a single occasion.
- Treatment of overdose: The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed. Studies in animals indicate that assisted respiration and the administration of a beta-blocker may be of value.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Tablet 200 mg, 300 mg, 400 mg, 600 mg and 800 mg cimetidine	carnauba wax, colloidal silicon dioxide, croscarmellose sodium, D&C Yellow No. 10 Lake 16%, ferric ferrous oxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

- CIMETIDINE 200 mg Tablets are pale green, round, biconvex, film-coated tablets, one side engraved APO over 200, other side plain. Available in bottles of 100 and 500 tablets.
- CIMETIDINE 300 mg Tablets are pale green, round, biconvex, film-coated tablets, one side engraved APO over 300, other side plain. Available in bottles of 100 and 1000 tablets.
- CIMETIDINE 400 mg Tablets are pale green, oval, biconvex, film-coated tablets, one side engraved APO-400, other side plain. Available in bottles of 100 and 500 tablets.
- CIMETIDINE 600 mg Tablets are pale green, oval, biconvex, film-coated tablets, one side engraved APO-600, other side plain. Available in bottles of 100 and 500 tablets.
- CIMETIDINE 800 mg Tablets are pale green, oval, biconvex, film-coated tablets, one side engraved APO-800, other side plain. Available in bottles of 100 and 500 tablets.

7 WARNINGS AND PRECAUTIONS

Gastrointestinal

Symptomatic response to cimetidine does not preclude the presence of a gastric malignancy. Cimetidine treatment can mask the symptoms and allow transient healing of gastric cancer. The potential delay in diagnosis should be borne in mind in patients of middle age or older with new or recently changed dyspeptic symptoms.

Renal

Because cimetidine is excreted by the kidney, a reduced dosage according to creatinine clearance should normally be administered to patients with impaired renal function. See 4.1 Dosing Considerations.

Circulating cimetidine levels are reduced by hemodialysis and cimetidine should be administered after hemodialysis treatment. See 4.1 Dosing Considerations.

No adjustment to the dosing regimen is necessary in patients undergoing peritoneal dialysis. See 4.1 Dosing Considerations.

Reproductive Health: Female and Male Potential

- **Fertility**

Reproduction studies performed in rats, mice and rabbits have revealed no evidence of impaired fertility or teratogenic risk due to cimetidine. See also: 7.1.1 Pregnant Women.

7.1 Special Populations

7.1.1 Pregnant Women

Experience to date with use of cimetidine in pregnant patients is limited. No significant adversities have been reported. Reproduction studies performed in rats, mice and rabbits have revealed no evidence of harm to the fetus due to cimetidine. Studies have demonstrated that cimetidine crosses the placental barrier.

Cimetidine should be used in pregnant or women of child-bearing potential only when, in the judgement of the physician, the anticipated benefits outweigh the potential risks.

Cimetidine has been used in clinical trials for the prevention of acid aspiration pneumonitis in women undergoing cesarean section or vaginal delivery without harm to the fetus.

7.1.2 Breast-feeding

Cimetidine is secreted in human milk. Adequate human data on use in lactation are not available. Cimetidine should be used in lactating patients only when, in the judgement of the physician, the anticipated benefits outweigh the potential risks.

7.1.3 Pediatrics

Pediatrics: Based on the data submitted and reviewed by Health Canada, the safety and efficacy of cimetidine in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use. See 1 INDICATIONS and 8.1 Adverse Reaction Overview.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following overview of adverse reactions contains information obtained from both clinical trials and post-market data.

Cardiovascular

Rare occurrences of sinus bradycardia, tachycardia, heart block and anaphylaxis have been reported in patients treated with H_2 antagonists.

CNS

Tiredness, and dizziness have been reported in a small number of patients during treatment with cimetidine.

A few cases of reversible confusional states have been reported, usually in elderly and/or severely ill patients, such as those with renal insufficiency or organic brain syndrome. These confusional states generally cleared within a few days of drug withdrawal.

Hallucination has been reported very rarely. Depression has been reported infrequently.

Endocrine

There have been reports that a few patients have developed reversible nonprogressive gynecomastia during prolonged treatment. No evidence of induced endocrine dysfunction was found, and the condition remained unchanged or returned toward normal with continuing cimetidine treatment. No effect of cimetidine (in recommended doses) on spermatogenesis, sperm count, motility or morphology has been found in double blind controlled studies. Fertilizing capacity has not been affected *in vitro*. Blood levels of androgen and gonadotropin were unchanged. Reversible impotence has been reported in rare instances.

Gastrointestinal

Mild and transient diarrhea have been reported in a small number of patients during treatment with cimetidine.

Hematologic

H_2 antagonist administration has been associated with the occurrence of leukopenia (including agranulocytosis), thrombocytopenia, pancytopenia, and aplastic anemia, as well as extremely rare reports of immune hemolytic anemia.

Investigations

Small increases of plasma creatinine have been reported. These did not progress with continued therapy and disappeared at the end of therapy. Some increases in serum transaminase and rare cases of hepatitis, fever, hypersensitivity vasculitis, interstitial nephritis, urinary retention and pancreatitis, which cleared on withdrawal of the drug, have been reported.

Musculoskeletal

There have been rare reports of reversible arthralgia and myalgia; exacerbation of joint symptoms in patients with pre-existing arthritis has also been reported. Such symptoms have usually been alleviated by a reduction in cimetidine dosage. Rare cases of polymyositis have been reported, but no causal relationship has been established.

Skin

Skin rashes, sometimes severe, including Stevens- Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma have been reported with H_2 receptor antagonists. Reversible alopecia has also been reported.

Other

Concomitant NSAID administration does not alter the incidence of adverse reactions resulting from therapy with cimetidine for those NSAIDs that have been tested.

Reported adverse reactions in children include neurotoxicity, and inhibition of hepatic microsomal metabolism. No change in adenohypophyseal secretion has been noted in studies in children receiving cimetidine. Cimetidine may produce transient cholestasis.

8.2 Clinical Trial Adverse Reactions

Information is not available.

8.5 Post-Market Adverse Reactions

Information is not available.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Cimetidine, apparently through an effect on certain microsomal enzyme systems, has on occasion caused clinically significant changes in the metabolism of some drugs; warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, lidocaine, diazepam, theophylline, and nifedipine; thereby delaying elimination and increasing blood levels of these drugs. Dosage of the drugs mentioned above and other similarly metabolized drugs, may require adjustment when starting or stopping concomitantly administered cimetidine, to maintain safe, optimum therapeutic blood levels. Such combinations should be administered with caution and patients should be observed closely.

Table 2- Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment
Chlordiazepoxide, Diazepam	C	Cimetidine has been shown to inhibit the liver microsomal metabolism of the benzodiazepines diazepam resulting in an increase in half-life and decrease in the clearance of the drug. The interaction with diazepam and chlordiazepoxide results in increased sedation.	Benzodiazepines that are metabolized other than via the hepatic system do not exhibit this effect.
Lidocaine	T	Elimination half-life, peak serum concentration, free drug concentration were all significantly increased when cimetidine was combined with lidocaine. Cimetidine also reduces hepatic blood flow and therefore may reduce the clearance of lidocaine.	This drug combination should be administered with caution and patients should be observed closely.
Nifedipine	C	Cimetidine significantly impairs nifedipine elimination and can produce greater physiologic responses to a given nifedipine dose.	This drug combination should be administered with caution and patients should be observed closely.
NSAIDs	T	No effect.	The concomitant administration of cimetidine and NSAIDs does not result in any impairment of the efficacy of a number of NSAIDs; however, not all currently marketed NSAIDs were tested.

Common name	Source of Evidence	Effect	Clinical comment
Phenytoin	C	Interaction with phenytoin has been reported to produce adverse clinical effects. Cimetidine increases serum phenytoin concentration, probably by inhibiting its metabolism.	Care should be taken in the concomitant use of cimetidine and phenytoin, and the dose of phenytoin should be modified according to the clinical symptoms and serum phenytoin concentrations.
Propranolol	C	Clearance of propranolol is decreased by concomitant cimetidine use. Resting pulse rates were also significantly lower during concomitant use.	This drug combination should be administered with caution and patients should be observed closely.
Theophylline	C	Cimetidine was found to slow the clearance of theophylline and extend its half-life.	This drug combination should be administered with caution and patients should be observed closely.
Warfarin anticoagulants	C	Clinically significant effects have been reported with the warfarin anticoagulants. The dose of cimetidine used may inhibit warfarin metabolism. Using warfarin together with cimetidine can cause you to bleed more easily.	Close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when cimetidine is administered concomitantly

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Cimetidine competitively inhibits the action of histamine at the histamine H_2 - receptor and thus is a histamine H_2 - receptor antagonists.

Cimetidine is not an anticholinergic agent. 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. Its ability to inhibit gastric acid secretion via this unique mechanism of action permits a new approach to the treatment of acid-related gastrointestinal disorders. In addition to its antisecretory effects, cimetidine also has cytoprotective properties.

In therapeutic studies, patients with NSAID-induced lesions or ulcers had symptomatic relief and healing when cimetidine was co-administered with the existing NSAID therapy.

Cimetidine is absorbed rapidly after oral administration. The plasma half-life is approximately two hours. The principal route of excretion is the urine.

The degree and duration of inhibition of basal and stimulated gastric acid secretion are dose-related; the data suggest that 80% or higher inhibition throughout a 24-hour period can be achieved by a dosage regimen of 1.2 g daily given in divided doses. Cimetidine 300 mg reduced total pepsin output as a result of the decrease in volume of gastric juice. The drug had no effect on the rate of gastric emptying or lower esophageal sphincter (LES) pressure.

10.2 Pharmacodynamics

Antisecretory Activity:

- **Basal Acid Secretion:** Cimetidine 300 mg inhibited basal gastric acid secretion by 100% for at least two hours and by at least 90% throughout the 4 hour study in fasting duodenal ulcer patients. The gastric pH in all subjects was increased to 5.0 or greater for at least 2-1/4 hours.
- **Nocturnal Acid Secretion:** Nighttime basal secretion in fasting duodenal ulcer patients was inhibited by a 300 mg dose of cimetidine by 100% for at least one hour and by a mean of 89% over a seven hour period. Gastric pH was increased to 5.0 or greater in most of the patients for three to four hours.
- **Food Stimulated Acid Secretion:** During the first hour after a standard experimental meal, cimetidine 300 mg inhibited gastric acid secretion in duodenal ulcer patients by at least 50% more than placebo and for the remaining two hours cimetidine inhibited gastric acid secretion by at least 75% more than placebo.

  The effect of a 300 mg breakfast dose of cimetidine continued for at least four hours and suppressed the early rise in gastric acid secretion following the luncheon meal in duodenal ulcer patients. This suppression of gastric acid output was maintained by another 300 mg dose of cimetidine given with lunch.

In another study, cimetidine 300 mg given with the meal increased gastric pH as compared with placebo (Table 3).

Table 3 MEAN GASTRIC pH

MEAN GASTRIC pH		
	Cimetidine	**Placebo**
1 hour	3.5	2.6
2 hours	3.1	1.6
3 hours	3.8	1.9
4 hours	6.1	2.2

The effect of cimetidine 300 mg vs propantheline bromide on food-stimulated gastric acid secretion was studied in duodenal ulcer patients. Propantheline bromide was titrated to maximally tolerated dosages - the average dose was 45 mg. Compared with placebo, cimetidine 300 mg reduced gastric acid output by 67% vs 27% for propantheline bromide.

Cimetidine 600 mg taken twice daily, at breakfast and bedtime, inhibited gastric acid secretion in duodenal ulcer patients over a 24 hour period to a significantly greater extent than 300 mg given four times daily.

Chemically Stimulated Acid Secretion: Cimetidine significantly inhibited gastric acid secretion

Stimulant	**Stimulant Dose**	**Cimetidine**	**% Inhibition**
Betazole	1.5 mg/kg (i.m.)	300 mg (p.o.)	85% at 2-½ hrs
Pentagastrin	6 mg/kg/hr (i.v.)	100 mg/hr (i.v.)	60% at 1 hr
Caffeine	5 mg/kg/hr (i.v.)	300 mg (p.o.)	100% at 1 hr
Insulin	0.03 units/ kg/hr (i.v.)	100 mg/hr (i.v.)	82% at 1 hr

The action of cimetidine on acid secretion is accomplished by reducing both acid concentration and the volume of gastric juice.

- **Pepsin Secretion:** Cimetidine 300 mg reduced total pepsin output as a result of the decrease in volume of gastric juice.
- **Intrinsic Factor Secretion:** Intrinsic factor secretion was studied with betazole as the stimulant. Cimetidine 300 mg inhibited the rise in intrinsic factor concentration produced by betazole, but some intrinsic factor was secreted at all times.
- **Serum Gastrin Secretion:** A single oral dose of cimetidine 300 mg augments the normal serum gastrin increase in response to a meal. This effect is probably attributable to the

action of the drug in inhibiting food-stimulated gastric acid secretion. Cimetidine does not increase nocturnal serum gastrin levels in fasting patients. Studies of serum gastrin levels in short-term therapy have shown a slight or no increase. Studies are continuing for evaluation of the long-term effects, if any, of cimetidine on serum gastrin.

Other Activities:

- **Gastric Mucosal Potential Difference**: When normal volunteers were given cimetidine (300 mg) alone, there was a significant rise in gastric mucosal potential difference.

  Acetylsalicylic acid (ASA) generally causes gastric potential difference to drop below basal levels. However, when volunteers were given cimetidine, gastric potential difference remained at or above basal levels even after the ingestion of ASA. Gastric mucosal biopsy of the control group revealed that at the time when ASA had caused the greatest drop in gastric potential difference, 20% of the cells were damaged. In subjects given cimetidine and then given ASA, gastric biopsy demonstrated that only 4% of the cells were damaged.

  The significance of these observations is not clearly understood, but some experts believe the changes in gastric mucosal potential difference reflect corresponding changes in the integrity of the gastric mucosal potential difference reflect corresponding changes in the integrity of the gastric mucosal barrier.

- **Lower Esophageal Sphincter Pressure and Gastric Emptying**: Cimetidine has no effect on the rate of gastric emptying or lowering esophageal sphincter (LES) pressure.

See SECTION 16 NON-CLINICAL TOXICOLOGY for non-clinical pharmacodynamic study data.

10.3 Pharmacokinetics

Absorption

Cimetidine is well absorbed from the gut in rats and dogs. In the dog, peak blood levels were reached in one to four hours following a single oral dose. The half-life in blood was estimated to be about 2 hours; measurable concentrations were still present after 24 hours. In rats, peak blood levels (lower than those observed in dogs) occurred within 1-2 hours after dosing.

Cimetidine is rapidly absorbed after oral administration.

Distribution:

Percentage of drug bound to plasma proteins was 24.9% in the rat, 16.2% in the dog, and 22.5% in human blood.

Distribution and residue studies in the rat indicated that, following oral dosing, the highest early drug concentrations were found in the liver and kidney. A small amount of label was found in the testes only on the first day after dosing. All tissues were substantially free of label by Day 7. Following intravenous dosing, cimetidine was rapidly eliminated from most body tissue, with little residual radioactivity being detected 24 hours after dosing.

The half-life of cimetidine is approximately 2 hours.

Metabolism:

Cimetidine failed to show significant enzyme-inducing activity in rats or dogs.

Elimination

Most of the drug is excreted unchanged in the urine; the principal metabolite in both rats and dogs is the sulfoxide, representing about 10% of recovered radioactivity in the dog, and 30% and 12% in male and female rats, respectively. Significant fecal excretion has been observed in the rat.

The principal route of excretion is in the urine.

Special Populations and Conditions

- **Pregnancy and Breast-feeding** Cimetidine crosses the placental barrier to enter the developing fetus and is secreted in the milk of lactating rats. Following cessation of dosing, drug concentration in milk falls rapidly.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15°C to 30°C.

CIMETIDINE should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

12 SPECIAL HANDLING INSTRUCTIONS

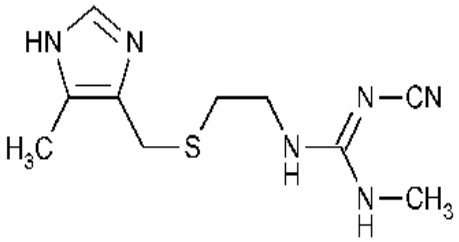
None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Cimetidine
Chemical name:	Guanidine, *N*''-cyano-*N*-methyl-*N*'-[2[[(5-methyl-1*H*-imidazol-4-yl)methyl]thio]ethyl-;
Molecular formula and molecular mass:	$C_{10}H_{16}N_6S$ and 252.35 g/mol
Structural formula:	Cimetidine



Physicochemical properties:	White to off-white odourless crystalline powder. Cimetidine has a melting point range of 141°-143°C. It is soluble in alcohol and in polyethylene glycol, freely soluble in methanol, sparingly soluble in isopropyl alcohol, slightly soluble in water and in chloroform, practically insoluble in ether.
Pharmaceutical standard:	USP

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicology Studies: The oral LD50 in rats and hamsters is over 3 g/kg; in mice the oral LD_{50} is over 2 g/kg. In dogs, the oral minimum lethal dose is 672 mg/kg; and the estimated median lethal dose is 2.6 g/kg.

Intravenous LD_{50}s are: in mice - males 137 mg/kg, females 162 mg/kg; in rats - males 113 mg/kg, females 99 mg/kg.

Intraperitoneal LD_{50}s are: in mice - males 431 mg/kg, females 378 mg/kg; in rats - males 686 mg/kg, females 543 mg/kg; and in hamsters - males 790 mg/kg, females 920 mg/kg.

Long-Term Toxicology Studies: In oral toxicity studies in rats and dogs for periods up to one year, similar species effects have been observed in all studies. Increased heart rate in dogs receiving the two top doses, 504 and 336 mg/kg, was observed early in the studies; this effect diminished as the studies progressed. In both species reduction in prostate weights was attributed to the weak antiandrogenic activity of the compound. In twelve-month studies, this effect in rats occurred at all dose levels (950, 378 and 150 mg/kg); in dogs it was observed at the three highest doses (504, 336, 144 mg/kg) but not at 41 mg/kg. Top dose rats also had smaller testes and seminal vesicles but no histopathological changes were observed in these tissues.

In the one-year study in rats the livers of top dose males and females were heavier than those of controls, and this is presumed to be due to increased metabolic work load. This effect was not associated with any biochemical or histological abnormalities. The dosed rats showed no significant differences from controls with regard to body weight, food consumption, hematology, clinical chemistry, urinalysis, or ophthalmoscopy.

In the one-year study in dogs, weight gain curves showed a dose-related depression; the curve for the lowest dose was very close to that of controls. Two dogs were killed before the end of the study (one in week 4, the other in week 33). Both had lost considerable weight, and histological examination showed nephropathy and centrilobular inflammatory cell infiltration in the liver in both dogs. Dogs killed at the end of one year showed no treatment-related changes in their livers. Occasional, but not progressive, elevations of some serum enzyme levels were seen in dogs given 504 and 336 mg/kg doses. The mean levels of serum enzymes in dosed groups were not significantly different from controls. There were no changes in hematology, urinalysis, ophthalmoscopy, or electrocardiography which could be related to drug treatment.

Pharmacodynamics: Cimetidine is a potent H_2-receptor antagonist *in vitro* and *in vivo*. It reduces basal gastric secretion in the rat and antagonizes histamine- and pentagastrin-stimulated secretion in the rat, cat and dog. In the Heidenhain pouch dog, blood levels correlated closely with inhibition of maximally stimulated gastric acid secretion, with values of 1-2 □M necessary for a 50% inhibitory effect. Administered to rats by intravenous infusion at dose levels (0.25 mg/kg/min) which produced up to 96% inhibition of basal gastric secretion, cimetidine had no effect on stomach motility; at ten times this dose, however, it abolished or caused marked reduction in motility. The drug has no effect on secretin-stimulated pancreatic secretion in the cat.

Detailed cardiovascular studies have shown that increased heart rate occurs in dogs at doses much higher than those which inhibit gastric secretion, and relatively much higher than the human dose. Propranolol prevented or reversed the increase in heart rate, suggesting that the mechanism by which cimetidine acts in this regard is an increase in sympathetic drive

specifically involving β-adrenergic receptors. Cimetidine had no effect on renal function.

Cimetidine has demonstrated a weak antiandrogenic effect. In animal studies, this was manifested as reduced prostate and seminal vesicle weights. However, there was no impairment of mating performance or fertility, nor any harm to the fetus in these animals at doses 9 to 56 times the full therapeutic dose of cimetidine, as compared with controls. Withdrawal of the drug in the adult animals resulted in recovery to control levels within 14 days. It has been concluded that this effect does not represent a potential clinical hazard. The drug exhibited no estrogenic activity in rats.

Carcinogenicity:

A 24-month oral toxicity and carcinogenicity study was carried out in rats, again using dose levels of 950, 378, and 150 mg/kg. Results were similar to those in the one-year study, except that rats at all three dose levels had smaller seminal vesicles; and rats dosed at 950 mg/kg had a low incidence of centrilobular hepatocellular vacuolation and hepatocellular enlargement, as well as higher incidences of atrophy of the seminiferous tubules, empty seminal vesicles and epididymes, and diminished secretory activity in the prostate. Cimetidine had no detectable effect on the histological appearance of the stomach or any other part of the gastrointestinal tract; this is of particular interest since the top-dose group had received, from the age of 8 weeks to 106 weeks, daily doses of cimetidine sufficient to prevent acid secretion for 24 hours. Lower incidences of pituitary (benign) and mammary tumours (benign and malignant) and a higher incidence of benign Leydig-cell tumours of the testes were found in treated rats than in controls. Exposure to cimetidine did not increase the risk of any kind of malignantneoplasm.

In these toxicity tests, the highest daily dose in rats was 950 mg/kg, and in dogs 504 mg/kg; the lowest doses were 150 and 41 mg/kg respectively. For comparison, a daily dose of 1200 mg in a 70 kg man is equivalent to 17 mg/kg.

Genotoxicity:

Information is not available.

Reproductive and Developmental Toxicology:

Cimetidine did not affect reproduction or fertility in female or male rats; the lack of effect in males indicates that the mild antiandrogenic action of the drug did not impair reproduction. Studies in three species (rat, mouse, rabbit) have shown no teratogenic effect attributable to cimetidine; and in peri- and post-natal studies in rats, the drug did not affect various litter parameters, or the early development of the young.

Special Toxicology:

Information is not available.

Juvenile Toxicity:

Information is not available.

17 SUPPORTING PRODUCT MONOGRAPHS

1) Tagamet® (cimetidine). Histamine H2 - Receptor Antagonist, Product Monograph, SmithKline Beecham Pharma Inc., June 28, 1999.

2) Tagamet® (cimetidine). Histamine H_2 Receptor Antagonist, CPS Monograph. IN: Gillis MC, Welbanks L, Bergeron D, et al, eds. Compendium of Pharmaceuticals and Specialities. Canadian Pharmacists Association, Ottawa, 1999; pp. 1737-1738.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]CIMETIDINE

Cimetidine tablets

Read this carefully before you start taking **CIMETIDINE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CIMETIDINE**.

What is CIMETIDINE used for?

CIMETIDINE is used in adults to:

- treat active sores in the upper part of the intestine (duodenum ulcers) and stomach (gastric ulcers).
- prevent intestinal or stomach ulcers from coming back after they have healed.
- treat Gastroesophageal Reflux Disease (GERD). This is a condition where the acid from the stomach persistently escapes into the food pipe causing pain, inflammation and heartburn.
- treat and relieve abnormal excessive acid secretion in the stomach caused by:
  - a tumour in the pancreas (Zollinger-Ellison syndrome).
  - too many mast cells building up in your body (systemic mastocytosis)
  - tumours in the parathyroid, pituitary glands and pancreas (multiple endocrine adenomas)
- treat and prevent lesions (ulcers, erosions) caused by non-steroidal anti-inflammatory drugs (NSAIDs) and gastrointestinal symptoms such as nausea, vomiting, abdominal pain, indigestion and chest pain.

CIMETIDINE is used in children (16 to 18 years of age) with cystic fibrosis to:

- manage their gastrointestinal symptoms. Cystic fibrosis is an inherited life-threatening disorder that damages the lungs and digestive tract.

How does CIMETIDINE work?

CIMETIDINE belongs to a group of medicines called Histamine H_2 receptor antagonists (H_2 blockers). It works by reducing the amount of acid produced by your stomach.

What are the ingredients in CIMETIDINE?

Medicinal ingredients: cimetidine

Non-medicinal ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, D&C Yellow No. 10 Lake 16%, ferric ferrous oxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

CIMETIDINE comes in the following dosage forms:

Tablets: 200 mg, 300 mg, 400 mg, 600 mg and 800 mg.

Do not use CIMETIDINE if:

- you are allergic to cimetidine or to any other ingredients in CIMETIDINE or its packaging.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CIMETIDINE. Talk about any health conditions or problems you may have, including if you:

- are middle-aged or over, with new or recently changed indigestion symptoms (e.g. stomach pain or discomfort, heartburn). Your healthcare professional will check if the cause of your symptoms is stomach cancer before starting treatment with CIMETIDINE.
- have kidney problems.
- are undergoing hemodialysis treatment.

Other warnings you should know about:

Pregnancy: CIMETIDINE is not recommended during pregnancy. If you discover that you are pregnant while taking CIMETIDINE, tell your healthcare professional **right away**. Only take CIMETIDINE during pregnancy if your healthcare professional has decided it is right for you and your baby.

Breastfeeding: CIMETIDINE passes into breast milk. CIMETIDINE is not recommended while breastfeeding. Only take CIMETIDINE while breastfeeding if your healthcare professional has decided it is right for you and your baby.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CIMETIDINE:

- chlordiazepoxide, a medicine used to treat anxiety and alcohol withdrawal.
- medicines used to prevent seizures (fits), such as phenytoin and diazepam.
- lidocaine, a medicine used to numb an area of your body to help reduce pain or discomfort caused by a procedure.
- medicines used to treat high blood pressure, such as propranolol and nifedipine.

- non-steroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and inflammation. This includes acetylsalicylic acid (ASA, or aspirin), ibuprofen, naproxen, and diclofenac.
- theophylline, a medicine used to treat asthma and other lung diseases.
- blood thinners, such as warfarin.

How to take CIMETIDINE:

- Take CIMETIDINE exactly as your healthcare professional tells you.
- Continue taking CIMETIDINE for the prescribed length of treatment even if you are feeling better. Stopping treatment too early may delay the healing process.
- Your healthcare professional may ask you to take other antacids during your treatment with CIMETIDINE.

Usual dose:

The dose of CIMETIDINE prescribed to you will depend on your condition. Your healthcare professional may change your dose depending on your response to CIMETIDINE.

- **To treat active intestinal or stomach ulcers:** The recommended adult dose is 800 to 1200 mg per day. It may be given as follows:
  - 800 mg once daily at bedtime; or
  - 600 mg twice daily, at breakfast and bedtime; or
  - 300 mg four times daily with meals and at bedtime.

  Take CIMETIDINE for at least 4 weeks if you have an intestinal ulcer or 6 weeks for a stomach ulcer unless otherwise instructed by your healthcare professional.

- **To prevent intestinal or stomach ulcers from coming back:** The usual adult dose is 400 mg once daily at bedtime, or 300 mg twice daily, at breakfast and bedtime. Take CIMETIDINE for at least 6 to 12 months.

- **To treat GERD:** The recommended adult dose is 1200 mg per day. It may be given as follows:
  - 800 mg once daily at bedtime; or
  - 600 mg twice daily, at breakfast and bedtime; or
  - 300 mg four times daily with meals and at bedtime.

  Take CIMETIDINE for 8 to 12 weeks.

- **To treat and relieve abnormal excessive acid secretion in the stomach caused by tumours or mast cell buildup:** The recommended adult dosage is 300 mg four times a day, with meals and at bedtime. Your healthcare professional will increase the dose based on your condition if necessary. The maximum dose is 2400 mg per day.

- **To treat and prevent lesions caused by NSAIDs and gastrointestinal symptoms:** The recommended adult dose is 800 mg once daily at bedtime or 400 mg twice daily, for 8 weeks. After the 8-week period, the recommended dose is 400 mg once daily at bedtime.

- **To manage gastrointestinal symptoms in children with cystic fibrosis:** Your healthcare professional will decide the right dose of CIMETIDINE for your child depending on their body weight.

Overdose:

If you think you, or a person you are caring for, have taken too much CIMETIDINE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget or miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the next dose as scheduled. Do not double the dose to make up for a missed dose.

What are possible side effects from using CIMETIDINE?

These are not all the possible side effects you may have when taking CIMETIDINE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- diarrhea
- feeling tired
- dizziness
- hair loss
- joint pain
- muscle pain
- breast growth in males
- impotence (inability to get or keep an erection). This side effect may be reversible after withdrawing the medicine. If you experience this side effect, continue taking CIMETIDINE and consult your healthcare professional. They may give you a different dose or prescribe you a different medicine.

CIMETIDINE can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Abnormally slow or fast heartbeat		√	
Fever	√		
Heart block (disturbances in the electrical system of the heart): slow or irregular heartbeat, shortness of breath, light-headedness, fainting, pain or discomfort in the chest, difficulty doing exercises			√
Hepatitis (inflammation of the liver): abdominal pain and swelling, fatigue, fever, nausea, vomiting, itchiness, light coloured stool, loss of appetite, dark urine, trouble thinking clearly, yellowing of the eyes and skin			√
Hypersensitivity vasculitis (allergic reaction leading to inflammation and damage to blood vessels, mainly in the skin): skin redness, red, brown or purple-coloured spots and patches on the skin, blistering of the skin or scabbing, swelling of the arms and legs, itchiness			√
Inability to pass urine or to empty the bladder			√
Nephritis (inflammation of the kidney): decreased appetite, difficulty breathing, fatigue, frequent urination, itchiness, nausea, vomiting			√
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen			√
Polymyositis (inflammatory muscle disease): muscle weakness, difficulty to climb stairs, rise from a seated position, lift objects or		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
reach overhead			
Severe allergic reactions: sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat, trouble breathing, collapse			√
Worsening of arthritis: joint pain and stiffness		√	
UNKNOWN FREQUENCY			
Anemias: • **Aplastic anemia** (your body stops producing enough new blood cells): tiredness, shortness of breath, pale skin. Severe disease may cause jaundice (yellowing of the eyes and skin) or abdominal discomfort. • **Autoimmune hemolytic anemia** (your immune system attacks and destroys your own red blood cells): tiredness, shortness of breath. Severe disease can cause bleeding, bruising, and infections.			√
Cholestasis in children (decrease in bile flow from the liver): jaundice (yellowing of the skin or whites of eyes), dark urine, light coloured stools		√	
Leukopenia / Agranulocytosis (decrease in white blood cells): frequent infection, fatigue, fever, aches, pains and flu-like symptoms			√
Mental health problems: • **depression** (sad mood that won't go away) • **hallucinations** (seeing, feeling or hearing things that are not there)		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
• **delirium** (worsening or sudden change in mental state, severe confusion)			
Neurotoxicity in children (damage to the nervous system): agitation, blurred vision, confusion, convulsions, difficulty speaking, dizziness, hallucinations, headache, impaired thinking, loss of control of body movements, memory loss, mental status changes, nervousness, numbness and tingling, vision loss, muscle weakness, seizures		√	
Pancytopenia (decrease in red and white blood cells and platelets): paleness of the skin, fatigue, rapid heart rate, shortness of breath, fever, and symptoms of infection such as cough, bruising easily and heavy bleeding			√
Serious Skin Reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma): redness, blistering and/or peeling of the skin, including the inside of the lips, eyes, mouth, nasal passages or genitals, swelling of the skin or serious skin rashes, raised red or purple skin patches, possibly with crust in the center, itchiness, burning sensation, can be accompanied with fever, chills, headache, cough, body aches or swollen glands, generally feeling unwell			√
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature (15°C to 30°C).
- If your healthcare professional tells you to stop taking CIMETIDINE, please return any leftover medicine to your pharmacist. CIMETIDINE should never be disposed of in your household trash.
- Keep out of reach and sight of children.

If you want more information about CIMETIDINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

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Last Revised FEB 10, 2022