PRODUCT MONOGRAPH

[Pr]NOVO-CIMETINE Tablets

Cimetidine
200 mg, 300 mg, 400 mg, 600 mg, and 800 mg

[Pr]NOVO-CIMETINE Injection

Cimetidine Hydrochloride Injection
300 mg/2 mL cimetidine

Histamine H2 Receptor Antagonist

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Date of Preparation:
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Control # 173478

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[Pr]NOVO-CIMETINE Tablets
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300 mg/2 mL cimetidine

THERAPEUTIC CLASSIFICATION
Histamine H_2 Receptor Antagonist

ACTION AND CLINICAL PHARMACOLOGY

Cimetidine competitively inhibits the action of histamine at the histamine H_2-receptor and thus represents a new class of pharmacological agents, the 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 2 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.

INDICATIONS AND CLINICAL USE

Novo-Cimetine (cimetidine) is primary therapy for conditions where the inhibition of gastric acid secretion is likely to be beneficial, such as:

- Duodenal ulcer therapy
- Nonmalignant gastric ulcer therapy
- Prophylaxis of recurrent duodenal or gastric ulcer

- Gastroesophageal reflux disease
- Management of upper gastrointestinal hemorrhage
- Pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and multiple endocrine adenomas
- Prophylaxis of stress ulceration
- Prophylaxis of acid aspiration pneumonitis
- Adjunctive therapy in the management of cystic fibrosis in children
- Treatment of NSAID-induced lesions (ulcers, erosions) and gastrointestinal symptoms and prevention of their recurrence

CONTRAINDICATIONS

Novo-Cimetine (cimetidine) is contraindicated in any patients who are known to have hypersensitivity to the drug.

PRECAUTIONS

Use in Pregnancy, Nursing Mothers
Experience to date with the 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 impaired fertility or harm to the fetus due to cimetidine. Studies have demonstrated that cimetidine crosses the placental barrier. It is also secreted in human milk. Cimetidine should be used in pregnant or lactating patients or women of childbearing 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.

Use in Impaired Renal Function
Because cimetidine is excreted by the kidney, a reduced dosage should normally be administered to patients with impaired renal function. (see DOSAGE AND ADMINISTRATION).

Drug Interactions
Cimetidine, apparently through an effect on certain microsomal enzyme systems, has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, lidocaine, diazepam, theophylline, and nifedipine; thereby delaying elimination and increasing blood levels of these drugs. Benzodiazepines that are metabolized other than via the hepatic system do not exhibit this effect. Since clinically significant effects have been reported with the warfarin anticoagulants, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when cimetidine is administered concomitantly. Interaction with phenytoin has also been reported to produce adverse clinical effects.

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.

The concomitant administration of cimetidine and NSAID's does not result in any impairment of the efficacy of a number of NSAID's; however, not all currently marketed NSAID's were tested.

Usage in Gastric Ulcer
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.

Rapid Intravenous Injection
Rapid intravenous injection should be avoided as there have been rare cases of cardiac arrhythmias and hypotension reported. (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

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

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 to 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.

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.

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.

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. Rare occurrences of

sinus bradycardia, tachycardia, heart block and anaphylaxis have been reported in patients treated with H2 antagonists.

Concomitant NSAID administration does not alter the incidence of adverse reactions resulting from therapy with cimetidine for those NSAID's 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.

There have been rare reports of reversible athralgia 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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In cases reported to date, involving oral ingestion of up to 20 g of cimetidine, no untoward effects have been noted and recovery has been uneventful.

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 may be of value.

DOSAGE AND ADMINISTRATION

Dosage
Adults: Cimetidine has been used in divided doses up to 2400 mg/day.

Children: For cimetidine administration in children, see "Pediatric Dosage".

Duodenal Ulcer and Nonmalignant Gastric Ulcer
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 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 nonmalignant gastric ulcer unless healing has been demonstrated by endoscopic examination.

While some patients may require concomitant antacids initially, Novo-Cimetine Tablets alone have been shown to promote rapid relief of symptoms.

Prophylaxis of Recurrent Duodenal or Gastric Ulcer
For most patients, the following regimens have been shown to be effective:

400 mg 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.

NSAID-Induced Lesions and Symptoms
The recommended adult dose of cimetidine is 800 mg per 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 at bedtime.

Gastroesophageal Reflux Disease
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 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, Novo-Cimetine Tablets alone promote rapid relief of symptoms.

Management of Upper Gastrointestinal Hemorrhage
In patients with upper gastrointestinal bleeding of sufficient magnitude as to require blood transfusions, Novo-Cimetine Injection should be administered parenterally, preferably by intravenous injection or intermittent infusion until 48 hours after active bleeding has stopped. At this time, an oral dosage regimen may be instituted.

Recommended Dosage for Oral Administration:
600 mg twice daily, at breakfast and bedtime
or
300 mg every 6 hours

Recommended Dosage for Intramuscular Injection:
300 mg every 6 hours.

Recommended Dosage for Intravenous Injection:
300 mg every 6 hours. Dilute 300 mg of Novo-Cimetine Injection in Sodium Chloride Injection, 0.9%, or other compatible intravenous solution to a total volume of 20 mL and inject slowly over a period of not less than two minutes. This method of administration should be avoided in patients with cardiovascular disease.

Recommended Dosage for Intermittent Intravenous Infusion:
300 mg every 6 hours. Dilute Novo-Cimetine Injection 300 mg in 50 or 100 mL of Dextrose Injection, 5%, Sodium Chloride Injection, 0.9% or other compatible intravenous solution and infuse over 15 to 20 minutes. (See **Parenteral Products).**

In some patients it may be necessary to increase dosage. When this is necessary, the increases should be made by more frequent administration of a 300 mg dose, but total daily dosage should not exceed 2400 mg.

Prophylaxis of Stress Ulceration
Recommended Adult Dosage: 300 mg intravenously every 6 hours, or more frequently to maintain a gastric pH above 4. (See recommendation for intravenous administration under Management of Upper Gastrointestinal Hemorrhage).

Pathological Hypersecretory Conditions (e. g. Zollinger-Ellison Syndrome)
Recommended Adult Oral Dosage: 300 mg four times per 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.

If intravenous administration is required, the dosage schedule should be the same as that recommended for control of upper gastrointestinal bleeding.

Prophylaxis of Acid Aspiration Pneumonitis
Recommended Adult Dosage:
In emergency surgery, including emergency cesarean section, 300 mg intramuscularly one hour before induction of anaesthesia and 300 mg intramuscularly or intravenously every 4 hours until patient responds to verbal commands.
In elective surgery, including elective cesarean section, same dosage as in emergency surgery, but oral cimetidine 300 mg may be started the night before the operation. For intravenous administration, see recommendation under **Management of Upper Gastrointestinal Hemorrhage.**

Dosage Adjustments 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 or by intravenous injection. Should the patient's condition require, the frequency of dosing may be increased to every eight 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 levels 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 coincides with the end of hemodialysis.

Peritoneal Dialysis
Peritoneal dialysis does not appear to remove cimetidine to any appreciable extent.

Pediatric Dosage
Intravenous or Oral Administration: When cimetidine is given intravenously to children, it should be injected or infused slowly over 10 to 20 minutes.

Children 1 to 12 years: 20 to 25 mg/kg/day in divided doses every 4 to 6 hours.

Children under 1 year: Data for use of cimetidine in children under one year of age are limited, but 20 mg/kg/day may be used in the absence of renal impairment.

In neonates under one week of age and in patients with moderate renal impairment, the suggested dose is 10 to 15 mg/kg/day in divided doses. The dosage may need to be reduced further in the presence of additional liver impairment or with severe renal impairment.

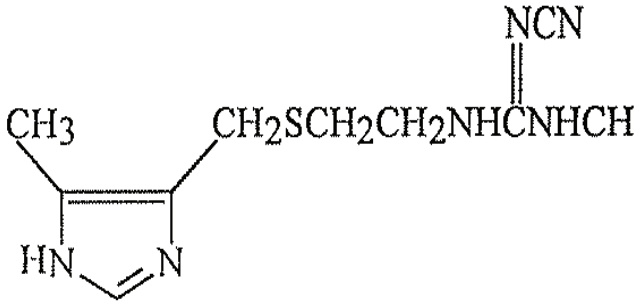
PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: cimetidine

Chemical Name: N''-cyano-N-methyl-N'-[2-[[(5-methyl-1Himidazol-4yl)methyl]thio]ethyl]guanidine

Structural Formula:



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

Molecular Weight: 252.34

Description: Cimetidine crystals melt at.139° to 144°C; solubility in water at 37°C is 1.14%.

Composition
Each Novo-Cimetine Tablet contains cimetidine 200 mg, 300 mg, 400 mg, 600 mg, or 800 mg.

Each millilitre of Novo-Cimetine Injection contains cimetidine hydrochloride equivalent to 150 mg of cimetidine with the following non-medicinal ingredients: Water for Injection, and hydrochloric acid and/or sodium hydroxide for pH adjustment.

Stability and Storage Recommendations
Store Novo-Cimetine Tablets between 15° - 30°C. Protect from light.

Store Novo-Cimetine Injection at controlled room temperature (15° - 25°C). Protect from light and do not refrigerate.

Parenteral Products
Dilute Novo-Cimetine Injection 300 mg in 50 or 100 mL of
- Dextrose Injection, 5%
- Dextrose Injection, 10%
- Sodium Chloride Injection, 0.9%

and infuse over 15 to 20 minutes.

Novo-Cimetine Injection is stable for 24 hours at normal room temperature when added to or diluted with the recommended intravenous solutions.

The diluted solution should be inspected visually for discolouration and particulate matter prior to administration. Discard unused portion.

AVAILABILITY OF DOSAGE FORMS

PrNovo-Cimetine Tablets are available as 200 mg, 300 mg, 400 mg, and 600 mg film-coated tablets in bottles of 100 and 1000 tablets and 800 mg film-coated tablets in bottles of 100 and 500 tablets.

PrNovo-Cimetine Tablets are also available as 300 mg, 400 mg, and 600 mg tablets in Unit Dose strips of 100.

PrNovo-Cimetine Injection is available as a 300 mg/2 mL cimetidine solution in clear glass single dose vials. Vials of 2 mL, packaged in 10's.

PHARMACOLOGY

Animal Pharmacology

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 μM necessary for a 50% inhibitory effect. Administered to rats by intravenous infusion at dose levels (0.25 mg/kg/minute) 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 intravenous 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 did not exhibit estrogenic activity in rats.

Metabolism

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 to 2 hours after dosing. Percentage of drug bound to plasma proteins was 24.9% in the rat, 16.2% in the dog, and 22.5% in human blood. 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.

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.

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.

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

Human Pharmacology
(A) Antisecretory Activity

1) Acid Secretion
Basal
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 2.25 hours.

Nocturnal
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
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:

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 versus 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% versus 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
Cimetidine significantly inhibited gastric acid secretion stimulated by exogenous histamine, pentagastrin, caffeine, and insulin as follows:

Stimulant	Stimulant Dose	cimetidine Dose	% Inhibition
Betazole	1.5 mg/kg (i.m.)	300 mg (p.o.)	85% at 2.5 hours
Pentagastrin	6 μg/kg/hr (i.v.)	100 mg/hr (i.v.)	60% at 1 hour
Caffeine	5 mg/kg/hr (i.v.)	300 mg (p.o.)	100% at 1 hour
Insulin	0.03 units kg/hr (i.v.)	100 mg/hr (i.v.)	82% at 1 hour

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

2) Pepsin Output
Cimetidine 300 mg reduced total pepsin output as a result of the decrease in volume of gastric juice.

3) Intrinsic Factor
Intrinsic factor secretion was studied with betazole as the stimulant. A 300 mg dose of cimetidine inhibited the rise in intrinsic factor concentration produced by betazole, but some intrinsic factor was secreted at all times.

4) Serum Gastrin
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 slight or no increase. Studies are continuing for evaluation of the long-term effects, if any, of cimetidine on serum gastrin.

(B) Other Activities

1) 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 that the changes in gastric mucosal potential difference reflect corresponding changes in the integrity of the gastric mucosal barrier.

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

(C) Pharmacokinetics
Cimetidine is rapidly absorbed after oral administration. The half-life of cimetidine is approximately 2 hours. The principal route of excretion is via the urine.

TOXICOLOGY

Acute Toxicity Studies
The oral LD_{50} 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 Toxicity 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 and 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.

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 malignant neoplasm.

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.

Reproductive Studies

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.

TOXICOLOGY SUMMARY

STUDY TYPE	SPECIES	DOSE	ROUTE	DURATION OF TREATMENT	PARAMETERS EVALUATED	RESULTS/OBSERVATIONS
Acute toxicity (LD_{50})	Rat	3000 mg/kg	oral	---	lethality	Death
		113 mg/kg (M) 99 mg/kg (F)	intravenous	--	lethality	Death occurred at 106 mg/kg. Death after intravenous dosing occurred within 5 minutes and it was preceded by tremor, hyperventilation, bradypnea, and convulsions indicating a central effect on respiration. Death from cardiac arrest did not occur until higher doses.
		686mg/kg (M) 543 mg/kg (F)	intraperitoneal	--	lethality	Death
	Mouse	>2000mg/kg	oral	--	lethality	Death
		137 mg/kg (M) 162 mg/kg (F)	intravenous	--	lethality	Death
		431 mg/kg (M) 378 mg/kg (F)	intraperitoneal	--	lethality	Death
	Hamster	>3000mg/kg	oral	--	lethality	Death
		790 mg/kg (M) 920 mg/kg (F)	intraperitoneal	--	lethality	Death
Acute toxicity	Dogs	672 mg/kg (minimum lethal dose)	Oral	--	lethality	Death
		2600 mg/kg (median lethal dose)	oral	--	lethality	Death
Acute toxicity	Beagle dogs	5-200 mg/kg	Intravenous (injection)	15 seconds	cardiovascular	Dosages up to 40 mg/kg caused marked tachycardia. Dosages of 62 mg/kg and greater caused **agitation, marked tachycardia** followed by bradycardia and death at 200 mg/kg. The minimum lethal dose is about 200 mg/kg,

STUDY TYPE	SPECIES	DOSE	ROUTE	DURATION OF TREATMENT	PARAMETERS EVALUATED	RESULTS/OBSERVATIONS
Acute toxicity	Dogs	30-250 mg/kg	Intravenous (injection)	I hour	Cardiovascular, local effects	No effects were observed at 30 mg/kg. At 200-250 mg/kg thrombi at injection sites and tachycardia were noted. The Minimum lethal dose was found to be about 240 mg/kg,
Long-term toxicity	Rats	950 mg/kg (highest) 150 mg/kg (lowest)	oral	12 months	Clinical effects	Reduction in prostate weights was attributed to the weak antiandrogenic activity of cimetidine. This effect in rats occurred at all dose levels (950, 378, and 150 mg/kg). Top-dose rats also had smaller testes and seminal vesicles but no histopathological changes were observed in these tissues. The livers of top-dose males and females were heavier than 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.

STUDY TYPE	SPECIES	DOSE	ROUTE	DURATION OF TREATMENT	PARAMETERS EVALUATED	RESULTS/OBSERVATIONS
Long-term toxicity	Dogs	504 mg/kg (highest) 41 mg/kg (lowest)	oral	12 months	Cardiovascular, histopathological, hematological, urinalysis	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. Reduction in prostate weights was attributed to the weak antiandrogenic activity of cimetidine. In dogs, this effect was observed at the three highest doses (504, 336 and 144mg/kg), but not at the lowest dose (41 mg/kg). Weight gain curves showed a dose-related depression; the curve for the lowest dose was very close to that of controls. Two dogs were sacrificed before the end of the study (one in week 4 and 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 sacrificed 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 336mg/kg. There were no changes in hematology, urinalysis, ophthalmoscopy, or electrocardiography which could be related to drug treatment.

STUDY TYPE	SPECIES	DOSE	ROUTE	DURATION OF TREATMENT	PARAMETERS EVALUATED	RESULTS/OBSERVATIONS
Long-term toxicity	Rats	126 mg/kg (maximum dose)	Intravenous (infusion)	10 days	hematological, urinalysis, blood chemical, histopathological,	No drug-related clinical effects and no effects on the evaluated parameters were noted.
Long-term toxicity	Rats	75 mg/kg (maximum dose)	Intravenous (injection)	14 days	Laboratory parameters	Raised serum cholesterol levels occurred in the top dose (75 mg/kg) rats. All other parameters remained within normal 1imits.
Long-term toxicity	Dogs	84 mg/kg (maximum dose)	Intravenous (infusion)	14 days	Clinical effects	Vomiting occurred in 2 of 6 top dose dogs. Weight loss occurred during the first week in the top dose dogs but in all other respects, the treated dogs did not differ from controls.
Long-term toxicity	Dogs	41 mg/kg (maximum dose)	Intravenous (injection)	14 days	Cardiovascular	Moderate tachycardia occurred in dogs receiving the maximum dose) dose of 41 mg/kg. Slight tachycardia occurred at lower doses but no other drug-related effects were reported.
Carcinogenicity	Rats	150 – 200 mg/kg/day	Oral (in drinking water)	12 months	Epithelial proliferation in the stomach	No histological evidence of malignant change and no effect on measurements of epithelial Proliferation by cimetidine in either fundus or antrum was noted.
Carcinogenicity	Rats	50 and 500 mg/kg of *N-nitroso cimetidine	gavage	12 months	Production of tumours, neoplasms, etc.	No evident treatment-related tumours were seen in rats receiving N-nitroso cimetidine.

STUDY TYPE	SPECIES	DOSE	ROUTE	DURATION OF TREATMENT	PARAMETERS EVALUATED	RESULTS/OBSERVATIONS
Carcinogenicity	Rats	0.5 mM of *N-nitroso cimetidine	Oral (in drinking water)	24onths	Production of tumours, neoplasms, etc., life span	The lifespan was not decreased and there was no significant increase in the incidence of any tumour.
Carcinogenicity	Rats	150, 378, 950 mg/kg	oral	24onths	Production of tumours or neoplasms, etc., organ weights, gastrointestinal tract	Rats at all three dose levels had smaller seminal vesicles. 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. There was no detectable effect on the histopathological appearance of the stomach or 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 versus control rats. Exposure to cimetidine did not increase the risk of malignant neoplasms.

STUDY TYPE	SPECIES	DOSE	ROUTE	DURATION OF TREATMENT	PARAMETERS EVALUATED	RESULTS/OBSERVATIONS
Carcinogenicity	Dogs	144 mg/kg daily cimetidine 1.14 mg/day nitrite and 37.3 mg/kg day nitrate	Oral	40 months	Production of tumours, neoplasms, etc., laboratory parameters, cardiovascular	All dogs became obese but no treatment related effects on hematological, clinical, chemistry, urinalysis, ophthalmoscopic, or electrocardiographic indices were observed in examinations done every 6 months for 3.5 years. Following biopsy of gastric mucosa, the only change found more often in treated dogs was congestion. No ulceration, epithelial or adenomatous hyperplasia, regenerative hyperplasia, metaplasia, dysplasia, cellular atypia or neoplasia was observed.
Reproduction, teratologic	Rats	4-240 mg/kg	Intravenous (injection or infusion)	1 day to 3 months	Reproductive, teratolgic	No serious adverse effects were noted with the exception of a reduction in the weights of the testes and secondary sex organs.
Reproduction, teratologic	Rats	0, 15, 75 mg/kg (16F, 16M per dose level)	Intravenous (rapid injection)	Short term	Organ weights, Clinical effects, Reproductive, teratologic	No clinical effects at the low dose were noted. With the high dose, tremors were observed. Prostate glands, seminal vesicles and testes at both dose levels were reduced in weight compared to controls.

STUDY TYPE	SPECIES	DOSE	ROUTE	DURATION OF TREATMENT	PARAMETERS EVALUATED	RESULTS/OBSERVATIONS
Reproduction, teratologic	Dogs	0, 8.4, 84 mg/kg (3F, 3M per dose level)	Intravenous (infusion)	14 days	Organ weights, Reproductive, teratologic	No systemic effects were noted. There was no significant alteration of weight of testes, prostate, or morphology of tissues. No mortalities were observed.
Reproduction, teratologic	Rats, mice, rabbits	100-950 mg/kg	oral	--	reproductive, teratologic	Cimetidine did not affect reproduction or fertility in female or male rats; the lack of effect in males indicates that the mild anti-androgenic action of the drug did not impair reproduction. Studies in rats, mice, and rabbits have shown no teratogenic effect attributable to cimetidine. The drug did not affect various litter parameters or the early development of the young in peri- and postnatal studies in rats.

* Nitroso derivative of cimetidine; (M) =males; (F) =females.

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