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ADVERSE REACTIONS

Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision and neuromuscular (extrapyramidal) reactions.

Neuromuscular (Extrapyramidal) Reactions

These symptoms are seen in a significant number of hospitalized mental patients. They may be characterized by motor restlessness, be of the dystonic type, or they may resemble parkinsonism.

Depending on the severity of symptoms, dosage should be reduced or discontinued. If therapy is reinstituted, it should be at a lower dosage. Should these symptoms occur in children or pregnant patients, the drug should be stopped and not reinstituted. In most cases barbiturates by suitable route of administration will suffice. (Or, injectable Benadryl®‖ may be useful.) In more severe cases, the administration of an anti-parkinsonism agent, except levodopa, usually produces rapid reversal of symptoms. Suitable supportive measures such as maintaining a clear airway and adequate hydration should be employed.

Motor Restlessness: Symptoms may include agitation or jitteriness and sometimes insomnia. These symptoms often disappear spontaneously. At times these symptoms may be similar to the original neurotic or psychotic symptoms. Dosage should not be increased until these side effects have subsided.

If this phase becomes too troublesome, the symptoms can usually be controlled by a reduction of dosage or change of drug. Treatment with anti-parkinsonian agents, benzodiazepines or propranolol may be helpful.

Dystonias: Symptoms may include: spasm of the neck muscles, sometimes progressing to torticollis; extensor rigidity of back muscles, sometimes progressing to opisthotonos; carpopedal spasm, trismus, swallowing difficulty, oculogyric crisis and protrusion of the tongue.

These usually subside within a few hours, and almost always within 24 to 48 hours, after the drug has been discontinued.

In mild cases, reassurance or a barbiturate is often sufficient. *In moderate cases,* barbiturates will usually bring rapid relief. *In more severe adult cases,* the administration of an anti-parkinsonism agent, except levodopa, usually produces rapid reversal of symptoms. Also, intravenous caffeine with sodium benzoate seems to be effective. *In children,* reassurance and barbiturates will usually control symptoms. (Or, injectable *Benadryl* may be useful.) Note: See *Benadryl* prescribing information for appropriate children's dosage. If appropriate treatment with anti-parkinsonism agents or *Benadryl* fails to reverse the signs and symptoms, the diagnosis should be reevaluated.

Pseudo-parkinsonism: Symptoms may include: mask-like facies; drooling; tremors; pill-rolling motion; cogwheel rigidity; and shuffling gait. Reassurance and sedation are important. In most cases these symptoms are readily controlled when an anti-parkinsonism agent is administered concomitantly. Anti-parkinsonism agents should be used only when required. Generally, therapy of a few weeks to 2 to 3 months will suffice. After this time patients should be evaluated to determine their need for continued treatment. (Note: Levodopa has not been found effective in pseudo-parkinsonism.) Occasionally it is necessary to lower the dosage of Stelazine (trifluoperazine HCl) or to discontinue the drug.

Tardive Dyskinesia: As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. The syndrome can also develop, although much less frequently, after relatively brief treatment periods at low doses. This syndrome appears in all age groups. Although its prevalence appears to be highest among elderly patients, especially elderly women, it is impossible to rely upon prevalence estimates to predict at the inception of neuroleptic treatment which patients are likely to develop the syndrome. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities. In rare instances, these involuntary movements of the extremities are the only manifestations of tardive dyskinesia. A variant of tardive dyskinesia, tardive dystonia, has also been described.

There is no known effective treatment for tardive dyskinesia; anti-parkinsonism agents do not alleviate the symptoms of this syndrome. If clinically feasible, it is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked.

It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time the syndrome may not develop.

Adverse Reactions Reported with Stelazine (trifluoperazine HCl) or Other Phenothiazine Derivatives: Adverse effects with different phenothiazines vary in type, frequency, and mechanism of occurrence, i.e., some are dose-related, while others involve individual patient sensitivity. Some adverse effects may be more likely to occur, or occur with greater intensity, in patients with special medical problems, e.g., patients with mitral insufficiency or pheochromocytoma have experienced severe hypotension following recommended doses of certain phenothiazines.

Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. (See WARNINGS.) Not all of the following adverse reactions have been observed with every phenothiazine derivative, but they have been reported with one or more and should be borne in mind when drugs of this class are administered: extrapyramidal symptoms (opisthotonos, oculogyric crisis, hyperreflexia, dystonia, akathisia, dyskinesia, parkinsonism) some of which have lasted months and even years—particularly in elderly patients with previous brain damage; grand mal and petit mal convulsions, particularly in patients with EEG abnormalities or history of such disorders; altered cerebrospinal fluid proteins; cerebral edema; intensification and prolongation of the action of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol), atropine, heat, organophosphorus insecticides; autonomic reactions (dryness of mouth, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis); reactivation of psychotic processes, catatonic-like states; hypotension (sometimes fatal); cardiac arrest; blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia, hemolytic anemia, aplastic anemia); liver damage (jaundice, biliary stasis); endocrine disturbances (hyperglycemia, hypoglycemia, glycosuria, lactation, galactorrhea, gynecomastia, menstrual irregularities, false-positive pregnancy tests); skin disorders (photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits.

EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed in some patients receiving phenothiazine tranquilizers. Although phenothiazines cause neither psychic nor physical dependence, sudden discontinuance in long-term psychiatric patients may cause temporary symptoms, e.g., nausea and vomiting, dizziness, tremulousness.

Note: There have been occasional reports of sudden death in patients receiving phenothiazines. In some cases, the cause appeared to be cardiac arrest or asphyxia due to failure of the cough reflex.

DOSAGE AND ADMINISTRATION—ADULTS

Dosage should be adjusted to the needs of the individual. The lowest effective dosage should always be used. Dosage should be increased more gradually in debilitated or emaciated patients. When maximum response is achieved, dosage may be reduced gradually to a maintenance level. Because of the inherent long action of the drug, patients may be controlled on convenient b.i.d. administration; some patients may be maintained on once-a-day administration.

When Stelazine (trifluoperazine HCl) is administered by intramuscular injection, equivalent oral dosage may be substituted once symptoms have been controlled.

Note: Although there is little likelihood of contact dermatitis due to the drug, persons with known sensitivity to phenothiazine drugs should avoid direct contact.

Elderly Patients: In general, dosages in the lower range are sufficient for most elderly patients. Since they appear to be more susceptible to hypotension and neuromuscular reactions, such patients should be observed closely. Dosage should be tailored to the individual, response carefully monitored, and dosage adjusted accordingly. Dosage should be increased more gradually in elderly patients.

Non-psychotic Anxiety

Usual dosage is 1 or 2 mg twice daily. Do not administer at doses of more than 6 mg per day or for longer than 12 weeks.

Psychotic Disorders

Oral: Usual starting dosage is 2 mg to 5 mg b.i.d. (Small or emaciated patients should always be started on the lower dosage.)

Most patients will show optimum response on 15 mg or 20 mg daily, although a few may require 40 mg a day or more. Optimum therapeutic dosage levels should be reached within 2 or 3 weeks.

When the Concentrate dosage form is to be used, it should be added to 60 mL (2 fl oz) or more of diluent *just prior to administration* to insure palatability and stability. Vehicles suggested for dilution are: tomato or fruit juice, milk, simple syrup, orange syrup, carbonated beverages, coffee, tea or water. Semisolid foods (soup, puddings, etc.) may also be used.

Intramuscular (for prompt control of severe symptoms): Usual dosage is 1 mg to 2 mg ($^1/_2$ to 1 mL) by deep intramuscular injection q4 to 6h, p.r.n. More than 6 mg within 24 hours is rarely necessary.

Only in very exceptional cases should intramuscular dosage exceed 10 mg within 24 hours. Injections should not be given at intervals of less than 4 hours because of a possible cumulative effect.

Note: Stelazine (trifluoperazine HCl) Injection has been usually well tolerated and there is little, if any, pain and irritation at the site of injection.

This solution should be protected from light. This is a clear, colorless to pale yellow solution; a slight yellowish discoloration will not alter potency. If markedly discolored, solution should be discarded.

DOSAGE AND ADMINISTRATION—PSYCHOTIC CHILDREN

Dosage should be adjusted to the weight of the child and severity of the symptoms. These dosages are for children, ages 6 to 12, who are hospitalized or under close supervision.

Oral: The starting dosage is 1 mg administered once a day or b.i.d. Dosage may be increased gradually until symptoms are controlled or until side effects become troublesome. While it is usually not necessary to exceed dosages of 15 mg daily, some older children with severe symptoms may require higher dosages.

Intramuscular: There has been little experience with the use of Stelazine (trifluoperazine HCl) Injection in children. However, if it is necessary to achieve rapid control of severe symptoms, 1 mg ($^1/_2$ mL) of the drug may be administered intramuscularly once or twice a day.

OVERDOSAGE

(See also under ADVERSE REACTIONS.) SYMPTOMS—Primarily involvement of the extrapyramidal mechanism producing some of the dystonic reactions described above. Symptoms of central nervous system depression to the point of somnolence or coma. Agitation and restlessness may also occur. Other possible manifestations include convulsions, EKG changes and cardiac arrhythmias, fever and autonomic reactions such as hypotension, dry mouth and ileus. TREATMENT—It is important to determine other medications taken by the patient since multiple dose therapy is common in overdosage situations. Treatment is essentially symptomatic and supportive. Early gastric lavage is helpful. Keep patient under observation and maintain an open airway, since involvement of the extrapyramidal mechanism may produce dysphagia and respiratory difficulty in severe overdosage. **Do not attempt to induce emesis because a dystonic reaction of the head or neck may develop that could result in aspiration of vomitus.** Extrapyramidal symptoms may be treated with anti-parkinsonism drugs, barbiturates, or *Benadryl.* See prescribing information for these products. Care should be taken to avoid increasing respiratory depression. If administration of a stimulant is desirable, amphetamine, dextroamphetamine or caffeine with sodium benzoate is recommended. Stimulants that may cause convulsions (e.g., picrotoxin or pentylenetetrazol) should be avoided.

If hypotension occurs, the standard measures for managing circulatory shock should be initiated. If it is desirable to administer a vasoconstrictor, *Levophed* and *Neo-Synephrine* are most suitable. Other pressor agents, including epinephrine, are not recommended because phenothiazine derivatives may reverse the usual elevating action of these agents and cause a further lowering of blood pressure.

Limited experience indicates that phenothiazines are *not* dialyzable.

HOW SUPPLIED

Tablets, 1 mg, 2 mg, 5 mg and 10 mg in bottles of 100.
1 mg 100's: NDC 0108-4903-20
2 mg 100's: NDC 0108-4904-20
5 mg 100's: NDC 0108-4906-20
10 mg 100's: NDC 0108-4907-20

Multi-Dose Vials, 10 mL (2 mg/mL), in 1's:
NDC 0108-4902-01

Concentrate (for institutional use), 10 mg/mL, in 2 fl oz bottles and in cartons of 12 bottles.

The Concentrate form is light-sensitive. For this reason, it should be protected from light and dispensed in amber bottles. *Refrigeration is not required.*

10 mg/mL 2 fl oz (carton of 12): NDC 0108-4901-42

Store all Stelazine (trifluoperazine HCl) formulations between 15° and 30°C (59° and 86°F).

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* norepinephrine bitartrate, Sanofi Winthrop Pharmaceuticals.

† phenylephrine hydrochloride, Sanofi Winthrop Pharmaceuticals.

‡ phenytoin, Parke-Davis.

§ metrizamide, Sanofi Winthrop Pharmaceuticals.

‖ diphenhydramine hydrochloride, Parke-Davis.

Veterans Administration/Military/PHS—Injection, 2 mg/mL, 10 mL, 1's, 6505-01-220-1479; Tablets, 1 mg, 100's, 6505-00-761-5658; 2 mg, 100's, 6505-01-361-5235; 5 mg, 100's, 6505-01-311-3784; 10 mg, 100's, 6505-01-246-1918.

SZ:L70

Shown in Product Identification Guide, page 339

TAGAMET® ℞

[tag 'ah-met]

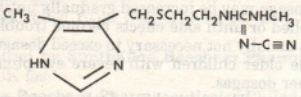
brand of cimetidine tablets
cimetidine hydrochloride liquid and
cimetidine hydrochloride injection

DESCRIPTION

Tagamet (cimetidine) is a histamine H_2-receptor antagonist. Chemically it is *N* ″-cyano- *N* -methyl-*N* ′-[2-[[(5-methyl-1 *H*-imidazol-4-yl) methyl] thio]-ethyl]-guanidine.

Continued on next page

The empirical formula for cimetidine is $C_{10}H_{16}N_6S$ and for cimetidine hydrochloride, $C_{10}H_{16}N_6SHCl$; these represent molecular weights of 252.34 and 288.80, respectively.



Cimetidine

Cimetidine contains an imidazole ring, and is chemically related to histamine.

(The liquid and injection dosage forms contain cimetidine as the hydrochloride.)

Cimetidine has a bitter taste and characteristic odor.

Solubility Characteristics: Cimetidine is soluble in alcohol, slightly soluble in water, very slightly soluble in chloroform and insoluble in ether. Cimetidine hydrochloride is freely soluble in water, soluble in alcohol, very slightly soluble in chloroform and practically insoluble in ether.

Tablets for Oral Administration: Each light green, film-coated tablet contains cimetidine as follows: 200 mg—round, imprinted with the product name TAGAMET, SKF and 200; 300 mg—round, debossed with the product name TAGAMET, SB and 300; 400 mg—oval Tiltab® tablets, debossed with the product name TAGAMET, SB and 400; 800 mg—oval Tiltab® tablets, debossed with the product name TAGAMET, SB and 800. Inactive ingredients consist of cellulose, D&C Yellow No. 10, FD&C Blue No. 2, FD&C Red No. 40, FD&C Yellow No. 6, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, povidone, propylene glycol, sodium lauryl sulfate, sodium starch glycolate, starch, titanium dioxide and trace amounts of other inactive ingredients.

Liquid for Oral Administration: Each 5 mL (1 teaspoonful) of clear, light orange, mint-peach flavored liquid contains cimetidine hydrochloride equivalent to cimetidine, 300 mg; alcohol, 2.8%. Inactive ingredients consist of FD&C Yellow No. 6, flavors, methylparaben, polyoxyethylene polyoxypropylene glycol, propylene glycol, propylparaben, saccharin sodium, sodium chloride, sodium phosphate, sorbitol and water.

Injection:

Single-Dose Vials for Intramuscular or Intravenous Administration: Each 2 mL contains, in sterile aqueous solution (pH range 3.8 to 6), cimetidine hydrochloride equivalent to cimetidine, 300 mg; phenol, 10 mg.

Multi-Dose Vials for Intramuscular or Intravenous Administration: 8 mL (300 mg/2 mL): Each 2 mL contains, in sterile aqueous solution (pH range 3.8 to 6), cimetidine hydrochloride equivalent to cimetidine, 300 mg; phenol, 10 mg.

Single-Dose Premixed Plastic Containers for Intravenous Administration: Each 50 mL of sterile aqueous solution (pH range 5 to 7) contains cimetidine hydrochloride equivalent to 300 mg cimetidine and 0.45 grams sodium chloride. No preservative has been added.

The plastic container is fabricated from specially formulated polyvinyl chloride. The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di 2-ethylhexyl phthalate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to the USP biological tests for plastic containers as well as by tissue culture toxicity studies.

ADD-Vantage®* Vials for Intravenous Administration: Each 2 mL contains, in sterile aqueous solution (pH range 3.8 to 6), cimetidine hydrochloride equivalent to cimetidine, 300 mg; phenol, 10 mg.

All of the above injection formulations are pyrogen free, and sodium hydroxide N.F. is used as an ingredient to adjust the pH.

CLINICAL PHARMACOLOGY

Tagamet (cimetidine) competitively inhibits the action of histamine at the histamine H_2 receptors of the parietal cells and thus is a histamine H_2-receptor antagonist.

Tagamet is not an anticholinergic agent. Studies have shown that *Tagamet* inhibits both daytime and nocturnal basal gastric acid secretion. *Tagamet* also inhibits gastric acid secretion stimulated by food, histamine, pentagastrin, caffeine and insulin.

Antisecretory Activity

1) **Acid Secretion:** *Nocturnal: Tagamet* 800 mg orally at bedtime reduces mean hourly H^+ activity by greater than 85% over an 8-hour period in duodenal ulcer patients, with no effect on daytime acid secretion. *Tagamet* 1600 mg orally h.s. produces 100% inhibition of mean hourly H^+ activity over an 8-hour period in duodenal ulcer patients, but also reduces H^+ activity by 95% for an additional 5 hours into the following morning. *Tagamet* 400 mg b.i.d. and 300 mg q.i.d. decrease nocturnal acid secretion in a dose-related manner, i.e., 47% to 83% over a 6- to 8-hour period and 54% over a 9-hour period, respectively.

Food Stimulated: During the first hour after a standard experimental meal, oral *Tagamet* 300 mg inhibited gastric acid secretion in duodenal ulcer patients by at least 50%. During the subsequent 2 hours *Tagamet* inhibited gastric acid secretion by at least 75%. The effect of a 300 mg breakfast dose of *Tagamet* continued for at least 4 hours and there was partial suppression of the rise in gastric acid secretion following the luncheon meal in duodenal ulcer patients. This suppression of gastric acid output was enhanced and could be maintained by another 300 mg dose of *Tagamet* given with lunch.

In another study, *Tagamet* 300 mg given with the meal increased gastric pH as compared with placebo.

	Mean Gastric pH	
	Tagamet	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

24-Hour Mean H^+ Activity: Tagamet 800 mg h.s., 400 mg b.i.d. and 300 mg q.i.d. all provide a similar, moderate (less than 60%) level of 24-hour acid suppression. However, the 800 mg h.s. regimen exerts its entire effect on nocturnal acid, and does not affect daytime gastric physiology.

Chemically Stimulated: Oral Tagamet (cimetidine) significantly inhibited gastric acid secretion stimulated by betazole (an isomer of histamine), pentagastrin, caffeine and insulin as follows:

Stimulant	Stimulant Dose	*Tagamet*	% Inhibition
Betazole	1.5mg/kg (sc)	300mg (po)	85% at $2^1/_2$ hours
Pentagastrin	6mcg/kg/hr (iv)	100mg/hr (iv)	60% at 1 hour
Caffeine	5mg/kg/hr (iv)	300mg (po)	100% at 1 hour
Insulin	0.03 units/kg/hr (iv)	100mg/hr (iv)	82% at 1 hour

When food and betazole were used to stimulate secretion, inhibition of hydrogen ion concentration usually ranged from 45% to 75% and the inhibition of volume ranged from 30% to 65%.

Parenteral administration also significantly inhibits gastric acid secretion. In a crossover study involving patients with active or healed duodenal or gastric ulcers, either continuous I.V. infusion of *Tagamet* 37.5 mg/hour (900 mg/day) or intermittent injection of *Tagamet* 300 mg q6h (1200 mg/day) maintained gastric pH above 4.0 for more than 50% of the time under steady-state conditions.

2) **Pepsin:** Oral *Tagamet* 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 a stimulant. Oral *Tagamet* 300 mg inhibited the rise in intrinsic factor concentration produced by betazole, but some intrinsic factor was secreted at all times.

*ADD-Vantage® is a trademark of Abbott Laboratories.

Other

Lower Esophageal Sphincter Pressure and Gastric Emptying

Tagamet has no effect on lower esophageal sphincter (LES) pressure or the rate of gastric emptying.

Pharmacokinetics

Tagamet is rapidly absorbed after oral administration and peak levels occur in 45 to 90 minutes. The half-life of *Tagamet* is approximately 2 hours. Both oral and parenteral (I.V. or I.M.) administration provide comparable periods of therapeutically effective blood levels; blood concentrations remain above that required to provide 80% inhibition of basal gastric acid secretion for 4 to 5 hours following a dose of 300 mg.

Steady-state blood concentrations of cimetidine with continuous infusion of *Tagamet* are determined by the infusion rate and clearance of the drug in the individual patient. In a study of peptic ulcer patients with normal renal function, an infusion rate of 37.5 mg/hour produced average steady-state plasma cimetidine concentrations of about 0.9 mcg/mL. Blood levels with other infusion rates will vary in direct proportion to the infusion rate.

The principal route of excretion of *Tagamet* is the urine. Following parenteral administration, most of the drug is excreted as the parent compound; following oral administration, the drug is more extensively metabolized, the sulfoxide being the major metabolite. Following a single oral dose, 48% of the drug is recovered from the urine after 24 hours as the parent compound. Following I.V. or I.M. administration, approximately 75% of the drug is recovered from the urine after 24 hours as the parent compound.

CLINICAL TRIALS

Duodenal Ulcer

Tagamet (cimetidine) has been shown to be effective in the treatment of active duodenal ulcer and, at reduced dosage, in maintenance therapy following healing of active ulcers.

Active Duodenal Ulcer: *Tagamet* accelerates the rate of duodenal ulcer healing. Healing rates reported in U.S. and foreign controlled trials with *Tagamet* are summarized below, beginning with the regimen providing the lowest nocturnal dose.

Duodenal Ulcer Healing Rates with Various *Tagamet* Dosage Regimens*

Regimen	300 mg q.i.d.	400 mg b.i.d.	800 mg h.s.	1600 mg h.s.
week 4	68%	73%	80%	86%
week 6	80%	80%	89%	—
week 8	—	92%	94%	—

* Averages from controlled clinical trials.

A U.S., double-blind, placebo-controlled, dose-ranging study demonstrated that all once-daily at bedtime (h.s.) *Tagamet* regimens were superior to placebo in ulcer healing and that *Tagamet* 800 mg h.s. healed 75% of patients at 4 weeks. The healing rate with 800 mg h.s. was significantly superior to 400 mg h.s. (66%) and not significantly different from 1600 mg h.s. (81%).

In the U.S. dose-ranging trial, over 80% of patients receiving *Tagamet* 800 mg h.s. experienced nocturnal pain relief after 1 day. Relief from daytime pain was reported in approximately 70% of patients after 2 days. As with ulcer healing, the 800 mg h.s. dose was superior to 400 mg h.s. and not different from 1600 mg h.s.

In foreign, double-blind studies with *Tagamet* 800 mg h.s., 79% to 85% of patients were healed at 4 weeks.

While short-term treatment with Tagamet (cimetidine) can result in complete healing of the duodenal ulcer, acute therapy will not prevent ulcer recurrence after *Tagamet* has been discontinued. Some follow-up studies have reported that the rate of recurrence once therapy was discontinued was slightly higher for patients healed on *Tagamet* than for patients healed on other forms of therapy; however, the *Tagamet*-treated patients generally had more severe disease.

Maintenance Therapy in Duodenal Ulcer: Treatment with a reduced dose of *Tagamet* has been proven effective as maintenance therapy following healing of active duodenal ulcers.

In numerous placebo-controlled studies conducted worldwide, the percent of patients with observed ulcers at the end of 1 year's therapy with *Tagamet* 400 mg h.s. was significantly lower (10% to 45%) than in patients receiving placebo (44% to 70%). Thus, from 55% to 90% of patients were maintained free of observed ulcers at the end of 1 year with *Tagamet* 400 mg h.s.

Factors such as smoking, duration and severity of disease, gender, and genetic traits may contribute to variations in actual percentages.

Trials of other anti-ulcer therapy, whether placebo-controlled, positive-controlled or open, have demonstrated a range of results similar to that seen with *Tagamet.*

Active Benign Gastric Ulcer

Tagamet has been shown to be effective in the short-term treatment of active benign gastric ulcer.

In a multicenter, double-blind U.S. study, patients with endoscopically confirmed benign gastric ulcer were treated with *Tagamet* 300 mg four times a day or with placebo for 6 weeks. Patients were limited to those with ulcers ranging from 0.5 to 2.5 cm in size. Endoscopically confirmed healing at 6 weeks was seen in significantly* more *Tagamet*-treated patients than in patients receiving placebo, as shown below:

	Tagamet	Placebo
week 2	14/63 (22%)	7/63 (11%)
total at week 6	43/65 (66%) *	30/67 (45%)

*$p<0.05$

In a similar multicenter U.S. study of the 800 mg h.s. oral regimen, the endoscopically confirmed healing rates were:

	Tagamet	Placebo
total at week 6	63/83 (76%) *	44/80 (55%)

*$p = 0.005$

Similarly, in worldwide double-blind clinical studies, endoscopically evaluated benign gastric ulcer healing rates were consistently higher with *Tagamet* than with placebo.

Gastroesophageal Reflux Disease

In two multicenter, double-blind, placebo-controlled studies in patients with gastroesophageal reflux disease (GERD) and endoscopically proven erosions and/or ulcers, *Tagamet* was significantly more effective than placebo in healing lesions. The endoscopically confirmed healing rates were:

Trial		*Tagamet* (800 mg b.i.d.)	*Tagamet* (400 mg q.i.d.)	Placebo	p-Value (800 mg b.i.d. vs. placebo)
1	Week 6	45%	52%	26%	0.02
	Week 12	60%	66%	42%	0.02
2	Week 6	50%		20%	<0.01
	Week 12	67%		36%	<0.01

In these trials *Tagamet* was superior to placebo by most measures in improving symptoms of day- and night-time

heartburn, with many of the differences statistically significant. The q.i.d. regimen was generally somewhat better than the b.i.d. regimen where these were compared.

Prevention of Upper Gastrointestinal Bleeding in Critically Ill Patients

A double-blind, placebo-controlled randomized study of continuous infusion cimetidine was performed in 131 critically ill patients (mean APACHE II score = 15.99) to compare the incidence of upper gastrointestinal bleeding, manifested as hematemesis or bright red blood which did not clear after adjustment of the nasogastric tube and a 5 to 10 minute lavage, persistent Gastroccult® positive coffee grounds for 8 consecutive hours which did not clear with 100 cc lavage and/or which were accompanied by a drop in hematocrit of 5 percentage points, or melena, with an endoscopically documented upper gastrointestinal source of bleed. 14% (9/65) of patients treated with cimetidine continuous infusion developed bleeding compared to 33% (22/66) of the placebo group. Coffee grounds was the manifestation of bleeding that accounted for the difference between groups. Another randomized, double-blind placebo-controlled study confirmed these results for an end point of upper gastrointestinal bleeding with a confirmed upper gastrointestinal source noted on endoscopy, and by post hoc analyses of bleeding episodes between groups.

Pathological Hypersecretory Conditions

(such as Zollinger-Ellison Syndrome)

Tagamet significantly inhibited gastric acid secretion and reduced occurrence of diarrhea, anorexia and pain in patients with pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and multiple endocrine adenomas. Use of *Tagamet* was also followed by healing of intractable ulcers.

INDICATIONS AND USAGE

Tagamet (cimetidine) is indicated in:

(1) Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks and there is rarely reason to use *Tagamet* at full dosage for longer than 6 to 8 weeks (see Dosage and Administration–Duodenal Ulcer). Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of *Tagamet* and antacids is not recommended, since antacids have been reported to interfere with the absorption of *Tagamet*.

(2) Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of active ulcer. Patients have been maintained on continued treatment with *Tagamet* 400 mg h.s. for periods of up to 5 years.

(3) Short-term treatment of active benign gastric ulcer. There is no information concerning usefulness of treatment periods of longer than 8 weeks.

(4) Erosive gastroesophageal reflux disease (GERD). Erosive esophagitis diagnosed by endoscopy. Treatment is indicated for 12 weeks for healing of lesions and control of symptoms. The use of *Tagamet* beyond 12 weeks has not been established (see Dosage and Administration—GERD).

(5) Prevention of upper gastrointestinal bleeding in critically ill patients.

(6) The treatment of pathological hypersecretory conditions (i.e., Zollinger-Ellison Syndrome, systemic mastocytosis, multiple endocrine adenomas).

CONTRAINDICATIONS

Tagamet is contraindicated for patients known to have hypersensitivity to the product.

PRECAUTIONS

General: Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of Tagamet (cimetidine hydrochloride) Injection by intravenous bolus.

Symptomatic response to *Tagamet* therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states (see Adverse Reactions) have been observed on occasion, predominantly, but not exclusively, in severely ill patients. Advancing age (50 or more years) and preexisting liver and/or renal disease appear to be contributing factors. In some patients these confusional states have been mild and have not required discontinuation of *Tagamet* therapy. In cases where discontinuation was judged necessary, the condition usually cleared within 3 to 4 days of drug withdrawal.

Drug Interactions: *Tagamet,* apparently through an effect on certain microsomal enzyme systems, has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, nifedipine, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole, thereby delaying elimination and increasing blood levels of these drugs.

Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when *Tagamet* is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either *Tagamet* 300 mg q.i.d. or 800 mg h.s. concomitantly with a 300 mg b.i.d. dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc.) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older. Data beyond 10 days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

Dosage of the drugs mentioned above and other similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered *Tagamet* to maintain optimum therapeutic blood levels.

Alteration of pH may affect absorption of certain drugs (e.g., ketoconazole). If these products are needed, they should be given at least 2 hours before cimetidine administration.

Additional clinical experience may reveal other drugs affected by the concomitant administration of *Tagamet.*

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month toxicity study conducted in rats, at dose levels of 150, 378 and 950 mg/kg/day (approximately 8 to 48 times the recommended human dose), there was a small increase in the incidence of benign Leydig cell tumors in each dose group; when the combined drug-treated groups and control groups were compared, this increase reached statistical significance. In a subsequent 24-month study, there were no differences between the rats receiving 150 mg/kg/day and the untreated controls. However, a statistically significant increase in benign Leydig cell tumor incidence was seen in the rats that received 378 and 950 mg/kg/day. These tumors were common in control groups as well as treated groups and the difference became apparent only in aged rats.

Tagamet (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 8 to 48 times the full therapeutic dose of *Tagamet,* as compared with controls. The cases of gynecomastia seen in patients treated for 1 month or longer may be related to this effect.

In human studies, *Tagamet* has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or *in vitro* fertilizing capacity.

Pregnancy: Teratogenic Effects. Pregnancy Category B: Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Tagamet.* There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Cimetidine is secreted in human milk and, as a general rule, nursing should not be undertaken while a patient is on a drug.

Pediatric Use: Clinical experience in children is limited. Therefore, *Tagamet* therapy cannot be recommended for children under 16, unless, in the judgment of the physician, anticipated benefits outweigh the potential risks. In very limited experience, doses of 20 to 40 mg/kg per day have been used.

Immunocompromised Patients: In immunocompromised patients, decreased gastric acidity, including that produced by acid-suppressing agents such as cimetidine, may increase the possibility of a hyperinfection of strongyloidiasis.

ADVERSE REACTIONS

Adverse effects reported in patients taking *Tagamet* are described below by body system. Incidence figures of 1 in 100 and greater are generally derived from controlled clinical studies.

Gastrointestinal: Diarrhea (usually mild) has been reported in approximately 1 in 100 patients.

CNS: Headaches, ranging from mild to severe, have been reported in 3.5% of 924 patients taking 1600 mg/day, 2.1% of 2,225 patients taking 800 mg/day and 2.3% of 1,897 patients taking placebo. Dizziness and somnolence (usually mild) have been reported in approximately 1 in 100 patients on either 1600 mg/day or 800 mg/day.

Reversible confusional states, e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation, have been reported predominantly, but not exclusively, in severely ill patients. They have usually developed within 2 to 3 days of initiation of *Tagamet* therapy and have cleared within 3 to 4 days of discontinuation of the drug.

Endocrine: Gynecomastia has been reported in patients treated for 1 month or longer. In patients being treated for pathological hypersecretory states, this occurred in about 4% of cases while in all others the incidence was 0.3% to 1% in various studies. No evidence of induced endocrine dysfunction was found, and the condition remained unchanged or returned toward normal with continuing Tagamet (cimetidine) treatment.

Reversible impotence has been reported in patients with pathological hypersecretory disorders, e.g., Zollinger-Ellison Syndrome, receiving *Tagamet,* particularly in high doses, for at least 12 months (range 12 to 79 months, mean 38 months). However, in large-scale surveillance studies at regular dosage, the incidence has not exceeded that commonly reported in the general population.

Hematologic: Decreased white blood cell counts in *Tagamet*-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 2 per million patients) and, very rarely, cases of pancytopenia or aplastic anemia have also been reported. As with some other H_2-receptor antagonists, there have been extremely rare reports of immune hemolytic anemia.

Hepatobiliary: Dose-related increases in serum transaminase have been reported. In most cases they did not progress with continued therapy and returned to normal at the end of therapy. There have been rare reports of cholestatic or mixed cholestatic-hepatocellular effects. These were usually reversible. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. However, as in the occasional liver injury with other H_2-receptor antagonists, in exceedingly rare circumstances fatal outcomes have been reported.

There has been reported a single case of biopsy-proven periportal hepatic fibrosis in a patient receiving *Tagamet.*

Rare cases of pancreatitis, which cleared on withdrawal of the drug, have been reported.

Hypersensitivity: Rare cases of fever and allergic reactions including anaphylaxis and hypersensitivity vasculitis, which cleared on withdrawal of the drug, have been reported.

Renal: Small, possibly dose-related increases in plasma creatinine, presumably due to competition for renal tubular secretion, are not uncommon and do not signify deteriorating renal function. Rare cases of interstitial nephritis and urinary retention, which cleared on withdrawal of the drug, have been reported.

Cardiovascular: Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists.

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

Integumental: Mild rash and, very rarely, cases of severe generalized skin reactions 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 been reported very rarely.

Immune Function: There have been extremely rare reports of strongyloidiasis hyperinfection in immunocompromised patients.

OVERDOSAGE

Studies in animals indicate that toxic doses are associated with respiratory failure and tachycardia that may be controlled by assisted respiration and the administration of a beta-blocker.

Reported acute ingestions orally of up to 20 grams have been associated with transient adverse effects similar to those encountered in normal clinical experience. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed.

There have been reports of severe CNS symptoms, including unresponsiveness, following ingestion of between 20 and 40 grams of cimetidine, and extremely rare reports following concomitant use of multiple CNS-active medications and ingestion of cimetidine at doses less than 20 grams. An elderly, terminally ill dehydrated patient with organic brain syndrome receiving concomitant antipsychotic agents and *Tagamet* 4800 mg intravenously over a 24-hour period experienced mental deterioration with reversal on *Tagamet* discontinuation.

There have been two deaths in adults who were reported to have ingested over 40 grams orally on a single occasion.

DOSAGE AND ADMINISTRATION

Duodenal Ulcer

Active Duodenal Ulcer: Clinical studies have indicated that suppression of nocturnal acid is the most important factor in duodenal ulcer healing (see Clinical Pharmacology—Acid Secretion). This is supported by recent clinical trials (see Clinical Trials—Active Duodenal Ulcer). Therefore, there is no apparent rationale, except for familiarity with use, for treating with anything other than a once-daily at bedtime dosage regimen (h.s.).

In a U.S. dose-ranging study of 400 mg h.s., 800 mg h.s. and 1600 mg h.s., a continuous dose response relationship for ulcer healing was demonstrated.

However, 800 mg h.s. is the dose of choice for most patients, as it provides a high healing rate (the difference between 800 mg h.s. and 1600 mg h.s. being small), maximal pain relief, a decreased potential for drug interactions (see Precautions—Drug Interactions) and maximal patient convenience. Patients unhealed at 4 weeks, or those with persistent symptoms, have been shown to benefit from 2 to 4 weeks of continued therapy.

It has been shown that patients who both have an endoscopically demonstrated ulcer larger than 1.0 cm and are

Continued on next page

also heavy smokers (i.e., smoke one pack of cigarettes or more per day) are more difficult to heal. There is some evidence which suggests that more rapid healing can be achieved in this subpopulation with *Tagamet* 1600 mg at bedtime. While early pain relief with either 800 mg h.s. or 1600 mg h.s. is equivalent in all patients, 1600 mg h.s. provides an appropriate alternative when it is important to ensure healing within 4 weeks for this subpopulation. Alternatively, approximately 94% of all patients will also heal in 8 weeks with *Tagamet* 800 mg h.s.

Other *Tagamet* regimens in the U.S. which have been shown to be effective are: 300 mg four times daily, with meals and at bedtime, the original regimen with which U.S. physicians have the most experience, and 400 mg twice daily, in the morning and at bedtime (see Clinical Trials—Active Duodenal Ulcer).

Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of *Tagamet* and antacids is not recommended, since antacids have been reported to interfere with the absorption of Tagamet (cimetidine).

While healing with *Tagamet* often occurs during the first week or two, treatment should be continued for 4 to 6 weeks unless healing has been demonstrated by endoscopic examination.

Maintenance Therapy for Duodenal Ulcer: In those patients requiring maintenance therapy, the recommended adult oral dose is 400 mg at bedtime.

Active Benign Gastric Ulcer

The recommended adult oral dosage for short-term treatment of active benign gastric ulcer is 800 mg h.s., or 300 mg four times a day with meals and at bedtime. Controlled clinical studies were limited to 6 weeks of treatment (see Clinical Trials). 800 mg h.s. is the preferred regimen for most patients based upon convenience and reduced potential for drug interactions. Symptomatic response to *Tagamet* does not preclude the presence of a gastric malignancy. It is important to follow gastric ulcer patients to assure rapid progress to complete healing.

Erosive Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dosage for the treatment of erosive esophagitis that has been diagnosed by endoscopy is 1600 mg daily in divided doses (800 mg b.i.d. or 400 mg q.i.d.) for 12 weeks. The use of *Tagamet* beyond 12 weeks has not been established.

Prevention of Upper Gastrointestinal Bleeding

The recommended adult dosing regimen is continuous I.V. infusion of 50 mg/hour. Patients with creatinine clearance less than 30 cc/min. should receive half the recommended dose. Treatment beyond 7 days has not been studied.

Pathological Hypersecretory Conditions
(such as Zollinger-Ellison Syndrome)

Recommended adult oral dosage: 300 mg four times a day with meals and at bedtime. In some patients it may be necessary to administer higher doses more frequently. Doses should be adjusted to individual patient needs, but should not usually exceed 2400 mg per day and should continue as long as clinically indicated.

Parenteral Administration

In hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or in patients who are unable to take oral medication, *Tagamet* may be administered parenterally.

The doses and regimen for parenteral administration in patients with GERD have not been established.

All parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Recommendations for parenteral administration:

Intramuscular injection: 300 mg q 6 to 8 hours (no dilution necessary). Transient pain at the site of injection has been reported.

Intravenous injection: 300 mg q 6 to 8 hours. 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 should not exceed 2400 mg per day. Dilute Tagamet (cimetidine hydrochloride) Injection, 300 mg, in Sodium Chloride Injection (0.9%) or another compatible I.V. solution (see Stability of *Tagamet* Injection) to a total volume of 20 mL and inject over a period of not less than 5 minutes (see Precautions).

Intermittent intravenous infusion: 300 mg q 6 to 8 hours, infused over 15 to 20 minutes. 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 should not exceed 2400 mg per day. **Vials:** Dilute *Tagamet* Injection, 300 mg, in at least 50 mL of 5% Dextrose Injection, or another compatible I.V. solution (see Stability of *Tagamet* Injection). **Plastic containers:** Use premixed *Tagamet* Injection, 300 mg, in 0.9% Sodium Chloride in 50 mL plastic containers. **ADD-Vantage® Vials:** Dilute contents of one vial in an ADD-Vantage® Diluent Container, available in 50 mL and 100 mL sizes of 0.9% Sodium Chloride Injection, and 5% Dextrose Injection.

Continuous intravenous infusion: 37.5 mg/hour (900 mg/day). For patients requiring a more rapid elevation of gastric pH, continuous infusion may be preceded by a 150 mg loading dose administered by I.V. infusion as described above. Dilute 900 mg *Tagamet* Injection in a compatible I.V. fluid (see Stability of *Tagamet* Injection) for constant rate infusion over a 24-hour period. *Note: Tagamet may be diluted in 100 to 1000 mL; however, a volumetric pump* is recommended if the volume for 24-hour infusion is less than 250 mL. In one study in patients with pathological hypersecretory states, the mean infused dose of cimetidine was 160 mg/hour with a range of 40 to 600 mg/hour. These doses maintained the intragastric acid secretory rate at 10 mEq/hour or less. The infusion rate should be adjusted to individual patient requirements.

DIRECTIONS FOR USE OF TAGAMET (cimetidine hydrochloride) INJECTION IN PLASTIC CONTAINERS

To open: Tear overwrap down side at slit and remove solution containers.

Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect solution quality or safety. The opacity will diminish gradually.

Do not add other drugs to premixed *Tagamet* Injection in plastic containers.

CAUTION: Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired. Additives should not be introduced into this solution. Do not use if the solution is cloudy or precipitated or if the seal is not intact.

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Use sterile equipment.

Preparation for administration:

1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

DIRECTIONS FOR USE OF TAGAMET® INJECTION IN ADD-VANTAGE® VIALS are enclosed in ADD-Vantage® Vial packaging.

Stability of *Tagamet* Injection

When added to or diluted with most commonly used intravenous solutions, e.g., Sodium Chloride Injection (0.9%), Dextrose Injection (5% or 10%), Lactated Ringer's Solution, 5% Sodium Bicarbonate Injection, Tagamet (cimetidine hydrochloride) Injection should not be used after more than 48 hours of storage at room temperature.

Tagamet Injection premixed in plastic containers is stable through the labeled expiration date when stored under the recommended conditions.

Dosage Adjustment for Patients with Impaired Renal Function

Patients with severely impaired renal function have been treated with *Tagamet*. However, such usage has been very limited. On the basis of this experience the recommended dosage is 300 mg q 12 hours orally or by intravenous injection. Should the patient's condition require, the frequency of dosing may be increased to q 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 reduces the level of circulating *Tagamet*. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

Patients with creatinine clearance less than 30 cc/min. who are being treated for prevention of upper gastrointestinal bleeding should receive half the recommended dose.

HOW SUPPLIED

Tablets: Light green, film-coated as follows: 200 mg—round, imprinted with the product name TAGAMET, SKF and 200—tablets in bottles of 100; 300 mg—round, debossed with the product name TAGAMET, SB and 300—tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only); 400 mg—oval-shaped Tiltab®, debossed with the product name, TAGAMET, SB and 400—tablets in bottles of 60 and Single Unit Packages of 100 (intended for institutional use only); 800 mg—oval-shaped Tiltab®, debossed with the product name TAGAMET, SB and 800—tablets in bottles of 30 and Single Unit Packages of 100 (intended for institutional use only).

Store between 15° and 30°C (59° and 86°F); dispense in a tight light-resistant container.

200 mg 100's: NDC 0108-5012-20
300 mg 100's: NDC 0108-5013-20
300 mg SUP 100's: NDC 0108-5013-21
400 mg 60's: NDC 0108-5026-18
400 mg SUP 100's: NDC 0108-5026-21
800 mg 30's: NDC 0108-5027-13
800 mg SUP 100's: NDC 0108-5027-21

Liquid: Clear, light orange, mint-peach flavored, as follows: 300 mg/5 mL in 8 fl oz (237 mL) amber glass bottles; 300 mg/5 mL in single-dose units in packages of 10 (intended for institutional use only).

Store between 15° and 30°C (59° and 86°F); dispense in a tight light-resistant container.

300 mg/5 mL 8 fl oz: NDC 0108-5014-48
300 mg/5 mL SUP 10's: NDC 0108-5014-10

Injection:

Vials: 300 mg/2 mL in single-dose vials, in packages of 25, and in 8 mL multi-dose vials, in packages of 10 and 25.

Store between 15° and 30°C (59° and 86°F); do not refrigerate.

300 mg/2 mL Single-Dose Vials: NDC 0108-5017-16 (package of 25 vials)

300 mg/2 mL in 8 mL Multi-Dose Vials:
NDC 0108-5022-11 (package of 10 vials)
NDC 0108-5022-16 (package of 25 vials)

Single-Dose Premixed Plastic Containers: 300 mg in 50 mL of 0.9% Sodium Chloride in single-dose plastic containers, in packages of 4 units. No preservative has been added.

Exposure of the premixed product to excessive heat should be avoided. It is recommended the product be stored between 15° and 30°C (59° and 86°F). Brief exposure up to 40°C does not adversely affect the premixed product.

300 mg/50 mL SUP's: NDC 0108-5029-04

ADD-Vantage® Vials: 300 mg/2 mL in single-dose ADD-Vantage® Vials, in packages of 25.

Store between 15° and 30°C (59° and 86°F); do not refrigerate.

300 mg/2 mL: NDC 0108-5031-16 (package of 25 vials)

Tagamet (cimetidine hydrochloride) Injection premixed in single-dose plastic containers is manufactured for SmithKline Beecham Pharmaceuticals by Baxter Healthcare Corporation, Deerfield, IL 60015.

Veterans Administration/Military/PHS—Tablets, 300 mg 100's, 6505–01–050–3547; 300 mg, 500's, 6505-01-323-5256; 400 mg, 60's, 6505-01-176-0712; 400 mg, 500's, 6505-01-323-5255; 800 mg, 30's, 6505-01-291-8374.

TG:L92A

Shown in Product Identification Guide, page 339

TAZICEF®

R

[taz 'i-sef]

brand of ceftazidime for injection for intravenous or intramuscular use

DESCRIPTION

Ceftazidime is a semisynthetic, broad-spectrum, beta-lactam antibiotic for intravenous or intramuscular administration. It is the pentahydrate of Pyridinium, 1-[[7- [[(2- amino-4-thiazolyl) [(1-carboxy-1-methylethoxy) imino]acetyl] amino]-2-carboxy -8- oxo -5- thia-1-azabicyclo (4.2.0.) oct -2- en -3- yl] methyl]-,hydroxide,inner salt, [6R-[6α,7β(Z)]].

Its molecular formula is $C_{22}H_{22}N_6O_7S_2 \cdot 5H_2O$ and the molecular weight is 636.65.

Tazicef (ceftazidime for injection) is a sterile, dry, powdered mixture of ceftazidime pentahydrate and sodium carbonate. The sodium carbonate at a concentration of 118 mg/gram of ceftazidime activity has been admixed to facilitate dissolution. The total sodium content of the mixture is approximately 54 mg (2.3 mEq)/gram of ceftazidime activity.

Tazicef in sterile crystalline form is supplied in vials equivalent to 1 gram or 2 grams of anhydrous ceftazidime, in piggyback vials equivalent to 1 gram or 2 grams of anhydrous ceftazidime and ADD-Vantage® vials equivalent to 1 gram or 2 grams of anhydrous ceftazidime. Solutions of *Tazicef* range in color from light yellow to amber, depending upon the diluent and volume used. The pH of freshly reconstituted solutions usually ranges from 5.0 to 8.0.

CLINICAL PHARMACOLOGY

After intravenous administration of 500 mg and 1 gram doses of ceftazidime over 5 minutes to normal adult male volunteers, mean peak serum concentrations of 45 mcg/mL and 90 mcg/mL, respectively, were achieved. After intravenous infusion of 500 mg, 1 gram and 2 gram doses of ceftazidime over 20 to 30 minutes to normal adult male volunteers, mean peak serum concentrations of 42 mcg/mL, 69 mcg/mL and 170 mcg/mL, respectively, were achieved. The average serum concentrations following intravenous infusion of 500 mg, 1 gram and 2 gram doses to these volunteers over an 8-hour interval are given in Table 1.

Table 1

Ceftazidime IV Dosage	Serum Concentrations (mcg/mL)				
	0.5 hr.	1 hr.	2 hr.	4 hr.	8 hr.
500 mg	42	25	12	6	2
1 gram	60	39	23	11	3
2 grams	129	75	42	13	5

The absorption and elimination of ceftazidime were directly proportional to the size of the dose. The half-life following intravenous administration was approximately 1.9 hours. Less than 10% of ceftazidime was protein bound. The degree of protein binding was independent of concentration. There was no evidence of accumulation of ceftazidime in the serum in individuals with normal renal function following multiple intravenous doses of 1 gram and 2 grams every 8 hours for 10 days.

Following intramuscular administration of 500 mg and 1 gram doses of ceftazidime to normal adult volunteers, the mean peak serum concentrations were 17 mcg/mL and 39 mcg/mL, respectively, at approximately 1 hour. Serum concentrations remained above 4 mcg/mL for 6 and 8 hours after the intramuscular administration of 500 mg and 1 gram doses, respectively. The half-life of ceftazidime in these volunteers was approximately 2 hours.

The presence of hepatic dysfunction had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 grams intravenously every 8 hours for 5 days.