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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 reinstated, it should be at a lower dosage. Should these symptoms occur in children or pregnant patients, the drug should be stopped and not reinstated. 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, pruritus, 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 pentylentetrazol) 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).

\* 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, 6505-00-761-6558; 2 mg, 100's, 6505-01-361-5235; 5 mg, 100's, 6505-01-311-3784; 10 mg, 100's, 6505-01-246-1918.

Shown in Product Identification Guide, page 339

TAGAMET® [tag 'ah-met]

brand of cimetidine tablets cimetidine hydrochloride liquid and cimetidine hydrochloride injection

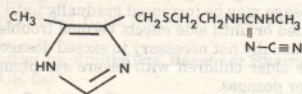
DESCRIPTION

Tagamet (cimetidine) is a histamine H2-receptor antagonist. Chemically it is N'-cyano-N-methyl-N'-[2-[(5-methyl-1H-imidazol-4-yl) methyl] thio]-ethyl]-guanidine.

Continued on next page

Information on the SmithKline Beecham Pharmaceuticals products appearing here is based on the labeling in effect on June 15, 1999. Further information on these and other products may be obtained from the Medical Department, SmithKline Beecham Pharmaceuticals, One Franklin Plaza, Philadelphia, PA 19101.

The empirical formula for cimetidine is C<sub>10</sub>H<sub>16</sub>N<sub>6</sub>S and for cimetidine hydrochloride, C<sub>10</sub>H<sub>16</sub>N<sub>6</sub>SHCl; 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<sub>2</sub> receptors of the parietal cells and thus is a histamine H<sub>2</sub>-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<sup>+</sup> 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<sup>+</sup> activity over an 8-hour period in duodenal ulcer patients, but also reduces H<sup>+</sup> activity by 35% 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 3-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 Taga-

met 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<sup>+</sup> 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	Dose	Tagamet	% Inhibition
Betazole	1.5mg/kg (sc)	300mg (po)	85% at 2 1/2 hours
		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.)		Placebo	p-Value (800 mg b.i.d. vs. placebo)
		Tagamet (800 mg b.i.d.)	Tagamet (400 mg q.i.d.)		
1	Week 6	45%	52%	26%	0.02
	Week 12	60%	66%	42%	0.01
2	Week 6	50%	20%	20%	<0.01
	Week 12	67%	36%	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 Gastrocult® 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. These neutropenic (agranulocytotic) episodes were usually

and, very rarely, cases of pancytopenia or aplastic anemia have also been reported. As with some other H<sub>2</sub>-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<sub>2</sub>-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<sub>2</sub>-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<sub>2</sub>-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.

#### DOSE 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

Information on the SmithKline Beecham Pharmaceuticals products appearing here is based on the labeling in effect on June 15, 1999. Further information on these and other products may be obtained from the Medical Department, SmithKline Beecham Pharmaceuticals, One Franklin Plaza, Philadelphia, PA 19101.

