CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

74-664

Generic Name: Cimetidine Hydrochloride Oral Solution 300 mg (base)/ 5mL

Sponsor: Hi-Tech Pharmacal Co., Inc.

Approval Date: October 28, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
74-664

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APPROVAL LETTER

ANDA 74-664

OCT 28 1997

Hi-Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

Dear Sir:

This is in reference to your abbreviated new drug application dated April 28, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cimetidine Hydrochloride Oral Solution, 300 mg (base)/5 mL.

Reference is also made to your amendments dated February 19, April 3, September 19, and October 6, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Cimetidine Hydrochloride Oral Solution, 300 mg (base)/5 mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Tagamet Oral Solution, 300 mg/5 mL of SmithKline Beecham Pharmaceuticals).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-664

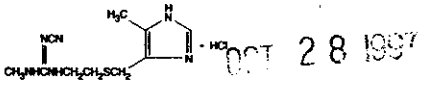
Final Printed Labeling

CIMETIDINE HYDROCHLORIDE ORAL SOLUTION

DESCRIPTION

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.

The molecular formula for cimetidine hydrochloride is $C_{10}H_{16}N_6S$·HCl and the molecular weight is 288.80. The structural formula of cimetidine hydrochloride is:



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

Cimetidine has a bitter taste and characteristic odor.

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

Each 5 mL (1 teaspoonful), for oral administration, contains cimetidine hydrochloride equivalent to cimetidine, 300 mg; alcohol, 2.8%. In addition, the oral solution contains the following inactive ingredients: FD&C Yellow No. 6, flavor, hydrochloric acid, methylparaben, polyoxyethylene polyoxypropylene glycol, propylene glycol, propylparaben, saccharin sodium, sodium chloride, dibasic sodium phosphate anhydrous, sorbitol and water. The pH range is 5.1 to 5.7.

CLINICAL PHARMACOLOGY

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.

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

Antisecretory Activity

1) **Acid Secretion:** *Nocturnal:* Cimetidine 800 mg orally at bedtime reduces mean hourly H^+ activity by greater than 85% over an eight-hour period in duodenal ulcer patients, with no effect on daytime acid secretion. Cimetidine 1600 mg orally h.s. produces 100% inhibition of mean hourly H^+ activity over an eight-hour period in duodenal ulcer patients, but also reduces H^+ activity by 35% for an additional five hours into the following morning. Cimetidine 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 six- to eight-hour period and 54% over a nine-hour period, respectively.

Food Stimulated: During the first hour after a standard experimental meal, oral cimetidine 300 mg inhibited gastric acid secretion in duodenal ulcer patients by at least 50%. During the subsequent two hours cimetidine inhibited gastric acid secretion by at least 75%.

The effect of a 300 mg breakfast dose of cimetidine continued for at least four 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 cimetidine given with lunch.

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

	Mean Gastric pH	
	Cimetidine	Placebo
1 hour	3.5	2.0
2 hours	3.8	2.0
3 hours	3.8	2.0
4 hours	4.1	2.0

24-Hour Mean H^+ Activity: Cimetidine 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 gives its entire effect on nocturnal acid, and does not affect daytime gastric physiology.

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

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

2) **Pepsin:** Oral cimetidine 300 mg reduced total pepsin output as a result of the decrease in volume of gastric juice.

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

Other

Lower Esophageal Sphincter Pressure and Gastric Emptying

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

Pharmacokinetics

Cimetidine is rapidly absorbed after oral administration and peak levels occur in 45 to 90 minutes. The half-life of cimetidine 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.

The principal route of excretion of cimetidine 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

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: Cimetidine accelerates the rate of duodenal ulcer healing. Healing rates reported in U.S. and foreign controlled trials with oral cimetidine are summarized below, beginning with the regimen providing the lowest nocturnal dose.

Duodenal Ulcer Healing Rates with Various Oral Cimetidine 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.) cimetidine regimens were superior to placebo in ulcer healing and that cimetidine 800 mg h.s. healed 75% of patients at four weeks. The healing rate with 800 mg h.s. was significantly superior to 400 mg h.s. (68%) and not significantly different from 1600 mg h.s. (81%).

In the U.S. dose-ranging trial, over 80% of patients receiving cimetidine 800 mg h.s. experienced nocturnal pain relief after one day. Relief from daytime pain was reported in approximately 70% of patients after two 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 cimetidine 800 mg h.s., 79 to 85% of patients were healed at four weeks.

While short-term treatment with cimetidine can result in complete healing of the duodenal ulcer, acute therapy will not prevent ulcer recurrence after cimetidine 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 cimetidine than for patients healed on other forms of therapy; however, the cimetidine-treated patients generally had more severe disease.

Maintenance Therapy in Duodenal Ulcer: Treatment with a reduced dose of cimetidine 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 cimetidine 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 cimetidine 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 cimetidine.

Active Benign Gastric Ulcer

Cimetidine 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 cimetidine 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 cimetidine-treated patients than in patients receiving placebo, as shown below:

	Cimetidine	Placebo
week 2	148/[illegible]	[illegible]

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

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	Mean Gastric pH	
	Cimetidine	Placebo
1 hour	3.5	2.1
2 hours	3.1	2.2
3 hours	1.8	2.2
4 hours	1.9	2.2

24-Hour Mean H^+ Activity: Cimetidine 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.

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

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	Cimetidine	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:

	Cimetidine	Placebo
total at week 6	53/83 (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 cimetidine 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, cimetidine was significantly more effective than placebo in healing lesions. The endoscopically confirmed healing rates were:

Trial		Cimetidine (800 mg b.i.d.)	Cimetidine (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 cimetidine 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.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome)

Cimetidine 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 cimetidine was also followed by healing of intractable ulcers.

INDICATIONS AND USAGE

Cimetidine Hydrochloride Oral Solution is indicated in:

(1) **Short-term treatment of active duodenal ulcer.** Most patients heal within 4 weeks and there is rarely reason to use cimetidine 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 oral cimetidine and antacids is not recommended, since antacids have been reported to interfere with the absorption of oral cimetidine.

(2) **Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of active ulcer.** Patients have been maintained on continued treatment with cimetidine 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 cimetidine beyond 12 weeks has not been established (see Dosage and Administration-GERD).

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

CONTRAINDICATIONS

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

PRECAUTIONS

General: Symptomatic response to cimetidine 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 cimetidine therapy. In cases where discontinuation was judged necessary, the condition usually cleared within 3 to 4 days of drug withdrawal.

Drug Interactions: Cimetidine, apparently through an effect on certain microsomal enzyme systems, has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, 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 cimetidine 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 cimetidine 300 mg q.i.d. or 800 mg h.s. concomitantly with a 300 mg b.i.d. dosage of theophylline extended-release tablets 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 ten 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 cimetidine 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 cimetidine.

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.

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 cimetidine as compared with controls. The cases of gynecomastia seen in patients treated for one month or longer may be related to this effect.

In human studies, cimetidine 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 cimetidine. 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 pediatric patients is limited. Therefore, cimetidine therapy cannot be recommended for pediatric patients 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 cimetidine 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 cimetidine therapy and have cleared within 3 to 4 days of discontinuation of the drug.

Endocrine: Gynecomastia has been reported in patients treated for one 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 cimetidine treatment.

Reversible impotence has been reported in patients with pathological hypersecretory disorders, e.g., Zollinger-Ellison Syndrome, receiving cimetidine, 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 cimetidine-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 3 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 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 cimetidine.

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 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 cimetidine 4800 mg intravenously over a 24-hour period experienced mental deterioration with reversal on Cimetidine discontinuation.

There have been two deaths in adults who have been reported to ingest 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-Antisecretory Activity-Acid Secretion). This is supported by recent clinical trials (see Clinical Pharmacology-Clinical Trials-Duodenal Ulcer-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. oral 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 two to four weeks of continued therapy.

It has been shown that patients who both have an endoscopically demonstrated ulcer larger than 1 cm and are 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 cimetidine 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 four weeks for this subpopulation. Alternatively, approximately 94% of all patients will also heal in eight weeks with cimetidine 800 mg h.s.

Other cimetidine 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 Pharmacology-Clinical Trials-Duodenal Ulcer-Active Duodenal Ulcer).

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

While healing with cimetidine 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.

related to this effect.

In human studies, cimetidine 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 cimetidine. 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 pediatric patients is limited. Therefore, cimetidine therapy cannot be recommended for pediatric patients 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 cimetidine 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 cimetidine therapy and have cleared within 3 to 4 days of discontinuation of the drug.

Endocrine: Gynecomastia has been reported in patients treated for one 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 cimetidine treatment.

Reversible impotence has been reported in patients with pathological hypersecretory disorders, e.g., Zollinger-Ellison Syndrome, receiving cimetidine, 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 cimetidine-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 3 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 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 cimetidine.

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 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 cimetidine 4800 mg intravenously over a 24-hour period experienced mental deterioration with reversal on Cimetidine discontinuation.

There have been two deaths in adults who have been reported to ingest 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-Antisecretory Activity-Acid Secretion). This is supported by recent clinical trials (see Clinical Pharmacology-Clinical Trials-Duodenal Ulcer-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. oral 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 two to four weeks of continued therapy.

It has been shown that patients who both have an endoscopically demonstrated ulcer larger than 1 cm and are 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 cimetidine 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 four weeks for this subpopulation. Alternatively, approximately 94% of all patients will also heal in eight weeks with cimetidine 800 mg h.s.

Other cimetidine 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 Pharmacology-Clinical Trials-Duodenal Ulcer-Active Duodenal Ulcer).

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

While healing with cimetidine 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 six weeks of treatment (see Clinical Pharmacology-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 cimetidine 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 cimetidine beyond 12 weeks has not been established.

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.

Dosage Adjustments for Patients with Impaired Renal Function

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

HOW SUPPLIED

Cimetidine Hydrochloride Oral Solution is a clear yellow, orange flavored solution containing 300 mg of cimetidine per 5 mL (teaspoonful) supplied in 8 fl oz (237 mL) amber PET containers NDC 50383-050-08 and 16 fl oz (473 mL) amber PET containers NDC 50383-050-16.

Store at controlled room temperature, 15°-30°C (59°-86°F).
Dispense in a tight, light-resistant container.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
HI-TECH PHARMACAL CO., INC.
Amityville, NY 11701

Rev. 5/96
MG #11913

H-T

NDC 50383-050-16

CIMETIDINE HYDROCHLORIDE ORAL SOLUTION 300 mg / 5 mL*

CAUTION: Federal law prohibits dispensing without prescription.

CIMETIDINE HYDROCHLORIDE ORAL SOLUTION 300 mg / 5 mL*

OCT 28

APPROVED

*Each 5 mL (1 teaspoonful) contains:

Cimetidine hydrochloride equivalent to cimetidine	300 mg
Alcohol	2.8%

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a tight, light-resistant container as defined in the USP.

Important: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.

Store at controlled room temperature 15°-30°C (59°-86°F).

7 40017-050-16 1

16 fl oz (473 mL)

HI-TECH PHARMACAL CO., INC.
Amityville, NY 11701

H-T

NDC 50383-050-08

CIMETIDINE HYDROCHLORIDE ORAL SOLUTION 300 mg / 5 mL*

CAUTION: Federal law prohibits dispensing without prescription.

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HI-TECH PHARMACAL CO., INC.
Amityville, NY 11701

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USUAL DOSAGE: See package insert for dosage and full prescribing information.

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Important: Use safety closures when dispensing this product unless otherwise directed by physician or requested by purchaser.

Store at controlled room temperature 15°-30°C (59°-86°F).

OCT 28

APPROVED

N 3 40017-050-08

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-664

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO.1

2. ANDA # 74-664

3. NAME AND ADDRESS OF APPLICANT
Hi Tech Pharmacal Co., Inc.
Attn: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

4. BASIS FOR SUBMISSION
The firm includes a patent certification statement. Patents for Cimetidine Hydrochloride held by Smith Kline Beecham expired on April 13, 1993 and May 17, 1994.

5. SUPPLEMENT(s)
NA

6. PROPRIETARY NAME
Tagamet

7. NONPROPRIETARY NAME
Cimetidine Hydrochloride Oral Solution

8. SUPPLEMENT(s) PROVIDE(s) FOR:
NA

9. AMENDMENTS AND OTHER DATES:
Original Submission April 28, 1995
Acknowledgement Letter June 2, 1995

10. PHARMACOLOGICAL CATEGORY
Antagonist

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA #17-924
DMF # —
DMF # —
DMF # —
DMF # —
DMF # —
DMF # —
DMF # —

13. DOSAGE FORM
Oral Solution

14. POTENCY
300 mg/5 mL

15. CHEMICAL NAME AND STRUCTURE
2-Cyano-1-methyl-3-[2-[[(5-methylimidazol-4-yl)methyl]thio]ethyl]-guanidine hydrochloride
Mol. Formula: $C_{10}H_{16}N_6S \cdot HCl$
Mol. Wt.: 288.80

16. RECORDS AND REPORTS
NA

17. COMMENTS
This application contains deficiencies. See comments in review.

18. CONCLUSIONS AND RECOMMENDATIONS
This application is unapprovable. Major amendment.

19. REVIEWER: Karen A. Bernard, Ph.D.
DATE COMPLETED: 7/1/95

Redacted 11

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1. CHEMIST'S REVIEW NO.2

2. ANDA # 74-664

3. NAME AND ADDRESS OF APPLICANT
Hi Tech Pharmacal Co., Inc.
Attn: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

4. BASIS FOR SUBMISSION
The firm includes a patent certification statement. Patents for Cimetidine Hydrochloride held by Smith Kline Beecham expired on April 13, 1993 and May 17, 1994.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Tagamet

7. NONPROPRIETARY NAME
Cimetidine Hydrochloride Oral Solution

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Original Submission	April 28, 1995
Acknowledgement Letter	June 2, 1995
FDA Deficiency Letter	August 4, 1995
Amendment Response	November 27, 1995

10. PHARMACOLOGICAL CATEGORY
Antagonist

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA #17-924
DMF # ——
DMF # ——
DMF # ——
DMF # ——
DMF # ——
DMF # ——
DMF # ——

13. DOSAGE FORM
Oral Solution

14. POTENCY
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15. CHEMICAL NAME AND STRUCTURE
2-Cyano-1-methyl-3-[2-[[(5-methylimidazol-4-yl)methyl]thio]ethyl]-guanidine hydrochloride
Mol. Formula: $C_{10}H_{16}N_6S \cdot HCl$
Mol. Wt.: 288.80

16. RECORDS AND REPORTS
N/A

17. COMMENTS
This application still contains deficiencies. See comments in review.

18. CONCLUSIONS AND RECOMMENDATIONS
This application is unapprovable.

19. REVIEWER:
Karen A. Bernard, Ph.D.

DATE COMPLETED:
3/1/95

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1. CHEMIST'S REVIEW NO.3

2. ANDA # 74-664

3. NAME AND ADDRESS OF APPLICANT
Hi Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

4. BASIS FOR SUBMISSION
The firm includes a patent certification statement. Patents for Cimetidine Hydrochloride held by SmithKline Beecham expired on April 13, 1993 and May 17, 1994.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Tagamet

7. NONPROPRIETARY NAME
Cimetidine Hydrochloride Oral Solution

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Original Submission	April 28, 1995
Acknowledgement Letter	June 2, 1995
FDA Deficiency Letter	August 4, 1995
Amendment Response	November 27, 1995
FDA Deficiency Letter	April 30, 1996
Amendment Response	June 12, 1996

10. PHARMACOLOGICAL CATEGORY
Antagonist

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA #17-924
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #

13. DOSAGE FORM
Oral Solution

14. POTENCY
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15. CHEMICAL NAME AND STRUCTURE
2-Cyano-1-methyl-3-[2-[[(5-methylimidazol-4-yl)methyl]thio]ethyl]-guanidine hydrochloride
Mol. Formula: $C_{10}H_{16}N_6S \cdot HCl$
Mol. Wt.: 288.80

16. RECORDS AND REPORTS
N/A

17. COMMENTS
This application still contains deficiencies.

18. CONCLUSIONS AND RECOMMENDATIONS
This application remains unapprovable.

19. REVIEWER: Karen A. Bernard, Ph.D.
DATE COMPLETED: 7/11/96

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confidential

commercial

information

1. CHEMIST'S REVIEW NO.4

2. ANDA # 74-664

3. NAME AND ADDRESS OF APPLICANT
Hi Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

4. BASIS FOR SUBMISSION
The firm includes a patent certification statement. Patents for cimetidine hydrochloride held by SmithKline Beecham expired on April 13, 1993 and May 17, 1994.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Tagamet

7. NONPROPRIETARY NAME
Cimetidine Hydrochloride Oral Solution

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Original Submission	April 28, 1995
Acknowledgement Letter	June 2, 1995
FDA Deficiency Letter	August 4, 1995
Amendment Response	November 27, 1995
FDA Deficiency Letter	April 30, 1996
Amendment Response	June 12, 1996
Amendment Response	September 17, 1996

10. PHARMACOLOGICAL CATEGORY
Antagonist

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA #17-924
DMF #
DMF #
DMF #
DMF #
DMF #
DMF #
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13. DOSAGE FORM
Oral Solution

14. POTENCY
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15. CHEMICAL NAME AND STRUCTURE
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Mol. Formula: $C_{10}H_{16}N_6S \cdot HCl$
Mol. Wt.: 288.80

16. RECORDS AND REPORTS
N/A

17. COMMENTS
See text of review.

18. CONCLUSIONS AND RECOMMENDATION
Not approvable; minor.

19. REVIEWER:
Andrew J. Langowski

DATE COMPLETED:
9/30/96

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1. CHEMIST'S REVIEW NO.5

2. ANDA # 74-664

3. NAME AND ADDRESS OF APPLICANT
Hi Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

4. BASIS FOR SUBMISSION
The firm includes a patent certification statement. Patents for cimetidine hydrochloride held by SmithKline Beecham expired on April 13, 1993 and May 17, 1994.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Tagamet

7. NONPROPRIETARY NAME
Cimetidine Hydrochloride
Oral Solution

9. AMENDMENTS AND OTHER DATES:

Original Submission	April 28, 1995
Acknowledgment Letter	June 2, 1995
FDA Deficiency Letter	August 4, 1995
Amendment Response	November 27, 1995
FDA Deficiency Letter	April 30, 1996
Amendment Response	June 12, 1996
Amendment Response	September 17, 1996
Amendment Response	February 19, 1997
Amendment Response	April 3, 1997
Amendment Response	Sep 19, 1997

10. PHARMACOLOGICAL CATEGORY
Antagonist

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA #17-924
DMF # ~~~
DMF # ~~~
DMF # ~~~
DMF # ~~~
DMF # ~~~
DMF # ~~~
DMF # ~~~

13. DOSAGE FORM
Oral Solution

14. POTENCY
300 mg/5 mL

15. CHEMICAL NAME AND STRUCTURE
2-Cyano-1-methyl-3-[2-[[(5-methylimidazol-4-yl)methyl]thio]ethyl]-guanidine hydrochloride
Mol. Formula: $C_{10}H_{16}N_6S \cdot HCL$ Mol. Wt.:288.80

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information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-664

BIOEQUIVALENCE REVIEW

NOV 4 1995

ANDA # 74-664
Cimetidine Hydrochloride
300 mg/5 mL Oral Solution
Reviewer: S.P. Shrivastava
WP #74664W.495

Hi-Tech Pharmacal Co., Inc
Amityville, NY
Submission Date:
April 28, 1995

Review of a Waiver Request

Cimetidine is a H_2 receptor antagonist. It competitively inhibits the action of histamine at the histamine H_2 receptor of parietal cells. It is indicated for the short-term treatments of active duodenal ulcer and active benign gastric ulcer, for maintenance therapy of duodenal ulcer, erosive gastroesophageal reflux disease, and for the treatment of pathological hypersecretory conditions.

Chemically cimetidine is N'-cyano-N-methyl-N'-[2-[[(5-methyl-1H-imidazol-4-yl)methyl]thio]-ethyl]-guanidine, with a molecular weight 252.34. It is soluble in alcohol, slightly soluble in water and insoluble in ether. The hydrochloride salt is soluble in alcohol and water but insoluble in ether.

Cimetidine is rapidly absorbed after oral administration, the peak levels appear in 45-90 minutes. The oral availability of drug is around 62%. Elimination is predominantly by renal route, around 62%. Protein binding is low (19%). The average systemic clearance and half-life is 8.3mL/min/kg and 2.0 hrs., respectively. The drug is widely used in the treatment of ulcers.

The firm is requesting a waiver of bioequivalence study requirements for the test product under 21 CFR 320.22(b)(3). The master formulation of the test product is shown below in comparison with the listed product, Tagamet Oral solution, manufactured by Smithkline Beecham.

The two formulations are qualitativly and quantitatively similar:

1. [redacted]

2. The test product contains [redacted] of sodium phosphate dibasic while the listed product contains [redacted] of [redacted]

   [redacted] has been reported to decrease the bioavailability of another H_2 receptor antagonist, ranitidine oral solution, by decreasing the small intestine transit time to 56% [see Pharm. Res. 10(7):1027-30 (1993)]. However, [redacted]

3. [redacted]

4. [redacted]

[Not for Release Under F.O.I.]

Table 1. Comparative Composition of Test and Reference Cimetidine Oral Solutions

Ingredient	Amount, mg/ 5 mL	
	Test Product	List Product
Cimetidine, USP	300.00	300.00[1]
Alcohol		
Hydrochloric acid		
FD&C Yellow No. 6		
Propylene Glycol, USP		
Methylparaben, NF		
Propylparaben, NF		
Sodium Saccharin, USP		
Sodium Chloride, USP		
Sodium Phosphate Dibasic, Anh., USP		
Sorbitol Solution		
Flavor		
Flavor		
Flavor		
Water		

APPEARS THIS WAY
ON ORIGINAL

5. The ANDA batch size is ——, and the proposed production batch size is ——

Deficiency Comment

None

Recommendation

The Division of Bioequivalence agrees that the information submitted by Hi-Tech Pharmacal Co., demonstrates that cimetidine hydrochloride oral solution, 300 mg base/5 mL, falls under 21 CFR Section 320.22 (b)(3) of the Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test oral solution formulation to be bioequivalent to Tagamet Oral Solution, 300 mg/5 mL, manufactured by Smithkline Beecham.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK /S/ 9/22/95

Concur: /S/ Date: 11/4/95

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

SPS/sps/9-9-95/74664W.495
cc: ANDA # 74-664 (Original, Duplicate), HFD-600 (DHare), HFD-630, HFC-130 (JAllen), HFD-655 (RNPatnaik, SPShrivastava), Drug File, Division File.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-664 SPONSOR : Hi-Tech.
DRUG & DOSAGE FORM : Cimetidine. Hcl, Oral Soln.
STRENGTH (s) : 300 mg/mL
TYPE OF STUDY: SD SDF MULT OTHER Waiver (1)
STUDY SITE: CLINICAL : ANALYTICAL :

STUDY SUMMARY :

Parameter	test	ref	ratio	90% CI (log).
Cmax(ng/ml)				
AUC(0-T) ngxhr/ml				
AUC(0-Inf)ngxhr/ml				
Tmax hr				
Half-life hr				

① Q1 + Q2 similar to Tagamet® oral Soln. (SKB)
② -
③ Test uses dibasic sodium phosphate instead of in Tagamet Soln.
④ Products are within IIG limits.
⑤ Waiver is granted.

DISSOLUTION :
Conditions

Time(min)	Test Mean(range)	Ref. Mean(range)
15		
30		
45		

Q =

PRIMARY REVIEWER : S. P. Shrivastava BRANCH : II

INITIAL : /S/ DATE : 12/8/95

BRANCH CHIEF : BRANCH :

INITIAL : /S/ DATE : 12/11/95

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL : /S/ DATE : 12/11/95

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL : N/A DATE :

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-664

ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE

HI TECH
369 BAYVIEW AVE
A[illegible]TYVILLE NY 11701

ANDA #: N074664

Dear Sir/Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for the following:

NAME OF DRUG:
CIMETIDINE HYDROCHLORIDE oral solution
Dosage Form: SOL Potency: 300 MG/ 5 ML USP:

DATE OF APPLICATION: 28-APR-95

DATE OF RECEIPT: 01-MAY-95

We will correspond with you further after we have had the opportunity to review the application.

However, in the interim, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the — active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

If the above methodology is not submitted, the review of the application will be delayed.

Please identify any communications concerning this application with the ANDA number shown above.

Sincerely yours,

Random III
amwine
HFD-645

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

file

DATE: JUL 11 1995

FROM: Chief
Investigations & Compliance Evaluation Branch, HFD-324

THRU: [redacted] Inspection Team, HFD-324

TO: Director
[redacted] & Technical Operations Branch, HFC-134

SUBJ: Profile Class Never Inspected
ANDA 74-664, Cimetidine HCl
Oral Solution, 300 mg/5mL

Applicant:
Hi-Tech Pharmacal Co.
369 Bayview Avenue
Amityville, NY 11701

PROFILE: CCS

REVIEWER: Karen Bernard
TELEPHONE: 301-594-1300

Establishment:
[redacted]

CFN #: None
DMF #: [redacted]

In connection with FDA's review of **ANDA 74-664**, please conduct an inspection of the above referenced foreign firm. **The application provides for this establishment to manufacture the drug substance for the above listed drug product.** For guidance, refer to CP 7346.832, Pre-Approval Inspections.

In preparing this assignment, we relied on the MPQAS drug quality assurance profile which reports that this firm has not been inspected for drug products in the referenced profile class. A GMP inspection is necessary unless there has been a recent inspection. If there has been recent coverage, or if the profile is not accurate, please call within one week to discuss the need for the inspection and update the QAP through the usual means.

In communicating with this office (FTS 301-827-0062), reference should be made to **ANDA 74-664**. Responses recommending approval should be forwarded as expeditiously as possible via facsimile (FAX) 301-827-0145 or EMS and should not wait for final report preparation and routing. Please direct your response to the attention of the Investigations & Compliance Evaluation Branch, HFD-324.

/S/

Mark A. Lynch

[ ] Approvable or [ ] Not Approvable per inspection of __/__/__
[ ] Scheduled EI __/__/__

signature

HFD-645 file

DATE: JUL 1 1 1995

TO: Director, New York District, HFR-NE100

FROM: Chief
Investigations & Compliance Evaluation Branch, HFD-324

SUBJ: Top 200 Inspection Request
ANDA 74-664, Cimetidine HCl Oral Solution, 300 mg/5 mL

PROFILE: LIQ & NEC

REVIEWER: Karen Bernard
TELEPHONE: 301-594-1300

Applicant:
Hi-Tech Pharmacal Co.
369 Bayview Avenue
Amityville, NY 11701

Establishments:
1. Hi-Tech Pharmacal Co.
369 Bayview Avenue
Amityville, NY 11701

2. Hi-Tech Pharmacal Co.
26 Edison Street
Amityville, NY 11701

CFN#: 2433247

In connection with FDA's review of **ANDA 74-664**, please conduct an inspection of the above referenced establishments. **The application provides for establishment #1 to manufacture and establishment #2 to test the above listed product. This is a Top 200 Drug Product, requiring a product specific inspection regardless of the last GMP EI covering the profile class LIQ.** For guidance, refer to CP 7346.832, Pre-Approval Inspections.

This application cannot be acted upon until the inspection is completed and your findings are reported to this office. Please call well in advance if you are unable to meet the time frame, whether due to priorities or the lack of readiness on the part of the firm.

Please send withhold and approval answers in the prescribed format via facsimile (FAX) 301-827-0145, or EMS, as soon as possible after the completion of the inspection, before the report write up starts. If classified OAI, recommend withhold and provide complete establishment inspection report with exhibits documenting deficiencies to HFD-324 **within 30 days.** If NAI recommend approval via EMS and forward endorsement (FD-481(E)-CG) by mail.

In communicating with this office (FTS 301-827-0062), reference should be made to **ANDA 74-664.** Please direct your written response to the Investigations & Compliance Evaluation Branch, HFD-324.

/S/
for Mark A. Lynch

Priority: **ANDA Pending**
Target Completion: AUG 1 1 1995

REVIEW OF PROFESSIONAL LABELING #1

ANDA

DRAFT

DATE OF REVIEW: July 11, 1995

ANDA #: 74-664

NAME OF FIRM: Hi-Tech Pharmacal Co., Inc.

NAME OF DRUG: Cimetidine Hydrochloride Oral Solution
300 mg base/5 mL

DATE OF SUBMISSION: April 28, 1995

COMMENTS:

CONTAINER: 8 fl oz and 16 fl oz

1. Revise the established name to read as follows:

   CIMETIDINE HYDROCHLORIDE ORAL SOLUTION

2. Place an asterisk following the expression of strength and immediately before the "Each 5 mL contains..." statement as follows:

   300 mg/5 mL*

   *Each 5 mL (1 teaspoonful) contains...

INSERT:

1. GENERAL COMMENTS

   a. Ensure that the "number" and the "unit of expression of strength" appear on the same line. [i.e., 800 mg, 1600 mg, etc.] Correct throughout the text of the insert.

   b. Please revise the insert so that you have consistent spacing between the section headings, subsection headings and sub-subsection headings and the text of the insert.

   c. Please revise the phrase "[redacted]" throughout the insert, so that there is a hyphen between the two words.

2. TITLE

   See comment 1 under CONTAINER.

3. DESCRIPTION

a. Revise the chemical name as follows:

...cyano-*N*-methyl...1*H*...

b. Revise paragraph 2 to read as follows:

The molecular formula for cimetidine hydrochloride is $C_{10}H_{16}N_6S \bullet HCl$ and the molecular weight is 288.80. The structural formula of cimetidine hydrochloride is:

c. Revise the chemical structure to be cimetidine hydrochloride.

d. Delete paragraph 4 [redacted]

e. Solubility Characteristics - Delete the first sentence.

f. Delete the title [redacted] and revise the paragraph to read as follows:

Each 5 mL (1 teaspoonful), for oral administration, contains cimetidine hydrochloride...2.8%. In addition, the oral solution contains the following inactive ingredients:...

g. Inactive ingredients

We note you have not included hydrochloric acid and [redacted] in your listing of inactive ingredients. We note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance). We believe this is an important public health measure. Please respond accordingly by correctly noting all the inactive ingredients present in this product. If you elect not to mention an inactive ingredient because it is a trade secret, you should use the phrase "and other ingredients", and provide supporting data concerning the "trade secret".

OK but not required for oral solutions. KB

4. CLINICAL PHARMACOLOGY

a. Antisecretory Activity, Chemically Stimulated Table

i. Correct the spelling of "Pentagastrin".

ii. Insert a space between the "number" and the "unit of expression of strength" throughout the text of the table. [i.e., 1.5 mg/kg]

iii. Insert a space between "%" and "Inhibition".

b. Chemically Stimulated - Delete the last paragraph. This information pertains to the intravenous dosage form only.

c. Pharmacokinetics - Delete paragraph 2 and the last sentence of paragraph 3. This information pertains to the intravenous dosage form only.

d. CLINICAL TRIALS - This is a subsection under CLINICAL PHARMACOLOGY. Please revise so that the title does not have the same prominence as section headings.

e. Active Duodenal Ulcer

i. Capitalize the "U" in "ulcer" that is in the sub-subsection title and in the Table heading.

ii. Insert "oral" in the following places:

(a) Paragraph 1, line 3 - ...with oral cimetidine...

(b) Table heading - ...Various Oral Cimetidine...

iii. Column one heading - "Regimen" rather than

f. Maintenace Therapy in Duodenal Ulcer

i. Delete the bold print from the subsubsection heading to be consistent with other subsubsection headings throughout the insert.

ii. Last sentence - Insert a space between "400" and "mg".

g. Active Benign Gastric Ulcer, last paragraph - Delete the italics from "cimetidine".

h. Gastroesophageal Reflux Disease

i. Delete the italics from "cimetidine" in paragraphs 1 and 3.

ii. Table - Insert a blank line/space between the

information in trial 1 and 2.

i. Delete the subsection [redacted]

j. Pathological Hypersecretory Conditions - Delete the italics from "cimetidine". [2 places]

5. INDICATIONS AND USAGE

a. Revise the first sentence to read:

Cimetidine tablets are indicated in:...

b. [redacted]

c. [redacted]

6. PRECAUTIONS

a. General

i. Delete paragraph 1. This information pertains to the intravenous dosage form only.

ii. Paragraph 3, line 5 - ...states have...

b. Drug Interactions

i. Paragraph 3, line 3 - Revise to read:

...theophylline extended-release tablets demonstrated...

ii. Insert the following text as the penultimate paragraph:

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.

c. Insert the following text to appear as the last subsection:

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.

7. ADVERSE REACTIONS

Insert the following text to appear as the last subsection:

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

8. DOSAGE AND ADMINISTRATION

a. Active Duodenal Ulcer

i. Paragraph 4 - Delete the [redacted] in "1 cm".

ii. Delete the space between paragraph 5 and 6. This should be one paragraph.

iii. Insert a space/blank line between paragraphs 7 and 8.

b. Active Benign Gastric Ulcer - Capitalize the "G" in "Gastric".

c. Delete the subsection [redacted]. This information pertains to the intravenous dosage form only.

d. Pathological Hypersecretory Conditions

i. Capitalize the "E" in "Ellison and the "S" in "Syndrome".

ii. Third line - ... "doses" ... (spelling).

e. Delete the subsection [redacted] This information pertains to the intravenous dosage form only.

f. Dosage Adjustment for Patients with Impaired Renal Function - Delete the last paragraph of this subsection.

9. HOW SUPPLIED

a. Second line

...containing 300 mg of cimetidine per...

b. Revise the storage temperature to read as follows:

...15° to 30°C (59° to 86°F).

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their container labels and package insert labeling, then prepare and submit draft container labels and insert labeling for review and comment.

NOTES TO CHEMIST:

1. See comment 3g under INSERT. Do you concur? ok but not required for oral solutions KB

2. [redacted]

FOR THE RECORD:

1. Review based on the labeling of the listed drug (Tagamet®;Revised July 1994; Approved February 22, 1995) and the labeling guidance for Cimetidine Tablets; Revised August 1994.

2. Patent/ Exclusivities:

   All patents and exclusivities for this dosage form have expired.

3. Storage Conditions/Dispensing Recommendations:

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

   ANDA - Store at CRT 15°-30° (59°-86°F). Dispense in a tight, light-resistant container as defined in the USP.

   USP - This drug product is not the subject of a USP monograph.

4. [redacted]

5. Product Line:

The innovator markets their product in 8 fl oz and in 5 mL single dose units in packages of 10.

The applicant proposes to market their product in 8 fl oz and one pint bottles.

6. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert is not consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 101 (Volume 1.1). See comment 3g under INSERT.

7. The description of the finished dosage form in the HOW SUPPLIED section is consistent with the finished product specs found on page 498 in Vol. 1.2.

8. Container/Closure

This product will be packaged in 8 and 16 oz amber glass bottles with click lock child-resistant closures.

cc: ANDA 74664
Dup/Division Fil /S/ 7/15/95
HFD-613/CZimmermann/MSchnitzke/JPhillips (no cc: /S/ /S/
HFD-600/RF
caz 7/12/95/REV/74664APR.95
Review
Final

for MC 7/18/95 7/19/95

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE *(Check One)* ☒ Original ☐ FollowUp ☐ FUR	DATE July 5, 1995	PHONE NO. 594-1300	EER ID #
REQUESTORS NAME:K. Bernard/K.Sherrod	DIVISION: Office of Generic Drugs		MAIL CODE: HFD-645
APPLICATION AND SUPPLEMENT NUMBER: ANDA 74-664			
BRAND NAME:	ESTABLISHED NAME: Cimetidine Hydrochloride Oral Solution		
DOSAGE STRENGTH: 300 mg/5 mL		STERILE ☐Yes ☒ No	
PROFILE CLASS:: LIQ	PRIORITY CLASSIFICATION *(See SMG CDER-4820.3)*		
APPLICANT'S NAME: Hi-Tech Pharmacal Co., Inc.			
APPLICANT'S ADDRESS: 369 Bayview Ave. Amityville, NY 11701			
COMMENTS :			

FACILITIES TO BE EVALUATED

(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY ~	
1. Applicant	Manufacturing facility	liq			
2. Applicant 26 Edison St. Amityville, NY 11701	Testing facility	nec			
3. [redacted]	[redacted]	ccs			
4. [redacted]	[redacted]	nec			
[redacted]	[redacted]	nec			

FOR HFD 324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.

x:\wpfile\eerforms\74664

FACILITIES TO BE EVALUATED *(Name and Complete Address)*	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY
[illegible]	[illegible]	nec		

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

Date of Review: March 1, 1996

ANDA Number: **74-664** Review Cycle: **2**

Dates of Submission:
- November 27, 1995 AC (Draft labels and labeling)
- November 27, 1995 AA (Side-by-side comparison)

Applicant's Name [as seen on 356(h)]: **Hi-Tech Pharmacal Co., Inc.**

Manufacturer's Name (If different than applicant): Same

Proprietary Name: None

Established Name: **Cimetidine Hydrochloride Oral Solution, 300 mg (base)/ 5 mL**

1° Reviewer: D.Konigstein

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE CHEMISTRY COMMENTS TO THE FIRM:

1. CONTAINER - 8 fl oz (237 mL) and 16 fl oz (473 mL)

   Revise the storage statement to read: Satisfactory in draft.

   Store at controlled room temperature 20-25°C (68-77°F) ~~[see USP]~~.

   OK. Kep.

2. INSERT

   a. DESCRIPTION

      i. ... cyano-*N*-methyl ... [cyano not italic, italic N].

      ii. Inactive Ingredients

         A). "flavor" [singular].

         B). "dibasic sodium phosphate anhydrous" rather than '

      iii. We encourage inclusion of the pH range.

X-1 drive corrected, DK 4/24/96

b. CLINICAL PHARMACOLOGY

i. Second paragraph, line 2 - Do not capitalize "cimetidine".

ii. Chemically Stimulated, Table - Please add sufficient spacing between the Stimulant Dose and Cimetidine columns. The "(iv)" on the Insulin line appears to be with the Cimetidine column.

iii. Pharmacokinetics, Duodenal Ulcer, Active Duodenal Ulcer - Capitalize the "U" in "ulcer" that is in the Table heading.

c. INDICATIONS AND USAGE

i. First sentence - We acknowledge an error in our August 4, 1995, letter which advised you to revise this to read "Cimetidine tablets are indicated in: ...". Please revise this sentence to read:

> Cimetidine Hydrochloride Oral Solution is indicated in: ...

ii. Short-term treatment of active duodenal ulcer, last sentence - insert "oral" before "cimetidine" in two locations.

d. PRECAUTIONS

i. General, second sentence - "rare" rather than

ii. Drug Interactions - Please insert a line space between paragraphs four and five.

iii. Pediatric Use - Use "pediatric patients" rather than ' ' in two locations.

e. ADVERSE REACTIONS

i. Hepatobiliary - Insert a line space between paragraphs one and two.

ii. Musculoskeletal - Do not capitalize "cimetidine".

iii. Integumental - ... Stevens-Johnson ... [spelling].

f. OVERDOSAGE

Third paragraph, last sentence - Delete excess space and do not capitalize "cimetidine" (two locations).

g. DOSAGE AND ADMINISTRATION

i. Duodenal Ulcer, Active Duodenal Ulcer

A). First paragraph

1). First sentence - ... healing (see Clinical Pharmacology-Antisecretory Activity-Acid Secretion).

2). Second sentence - ... trials (see Clinical Pharmacology-Clinical Trials-Duodenal Ulcer-Active Duodenal Ulcers). [note "trials" - spelling].

B). Second paragraph, line 1 - ... U.S. oral dose-ranging ...

C). Fifth paragraph - ... bedtime (see Clinical Pharmacology-Clinical Trials-Duodenal Ulcer-Active Duodenal Ulcers).

D). Seventh paragraph - ... for 4 to 6 weeks ... ["6" rather than ←

ii. Active Benign Gastric Ulcer

A). Line 4 - ... treatment (see Clinical Pharmacology-Clinical Trials) ...

B). Line 7 - Do not capitalize "cimetidine".

iii. Dosage Adjustment for Patients with Impaired Renal Function

A). First sentence - Do not capitalize "cimetidine".

B). Use "every" rather than ←

h. HOW SUPPLIED

~~i.~~ ← Please use "8 fl oz" and "16 fl oz" rather than "eight oz" and "one pint".

~~ii. See comment under CONTAINER.~~

X-1 drive corrected. DK 4/24/96

Please revise your labels and labeling, as instructed above, and submit final printed labels and labeling. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
PROPRIETARY NAME			X
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X

Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring:			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration? See FTR - Bio	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement? See FTR	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			X
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			X
Insert labeling references a food effect or a no-effect? If so, was a food study done? Products are rated AA. Waiver granted. See FTR			

Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			X

FOR THE RECORD:

1. BASIS OF REVIEW:

The reference listed drug labeling is Tagamet® SmithKline Beecham; Revised July 1994; Approved February 22, 1995. This is confirmed by the MIS system. Labeling guidance; Revised September 1995; for Cimetidine Tablets was also utilized except for the DESCRIPTION section which was based on Cimetidine Hydrochloride Injection since the Oral Solution is the salt form.

2. PACKAGING CONFIGURATIONS:

RLD: 237 mL amber glass bottles
5 mL single-dose units, 10s
The innovator no longer has a 400 mg/6.67 mL unit dose cup package. This was acknowledged in the approval letter for the current insert.

ANDA: The insert lists 237 mL and 473 mL available in amber PET with CRCs. Though on page 442 of original submission, the firm proposes the 8 fl oz size in both _____, and amber PET containers.

3. DISPENSING RECOMMENDATIONS

USP - Product is not a USP monograph.
ANDA - Dispense in a tight, light-resistant container as defined in the USP.
NDA - Dispense in a tight, light-resistant container.

4. STORAGE RECOMMENDATIONS
USP: Not a USP product.
NDA: Store between 15°-30°C (59°-86°)F.
ANDA: Store at CRT 15°-30°C (59°-86°F).

Per 11-16-95 Memo titled Uniform Storage Statements in Drug Substance and Drug Product Labeling, authored by Dr. Poochikian, Chairman of the CDER Stability Committee, the comment was made to revise the storage statement to "Store at controlled room temperature 20-25°C (68-77°F) [see USP]."

5. INACTIVE INGREDIENTS/ BIOEQUIVALENCY ISSUES: The formulations are slightly different. See Bio waiver

granted 11-4-95 listing comparison against RLD for ingredients.

6. PATENT/EXCLUSIVITY ISSUES: No patents or exclusivities exist for Cimetidine Hydrochloride Oral Solution.

7. ALCOHOL

Per composition statement, 0.15 mL of Alcohol USP per 5 mL which equals 0.03 mL alcohol contained in 1 mL.

A little over — claimed. Probably some —

8. Regarding DOSAGE AND ADMINISTRATION comments - It was noted the innovator's labeling did not expand the references to other sections entirely. These comments reflect the actual section/subsection(s) headings. Usually, we prefer to have the section headings capitalized in such references, however the comment wasn't made in review one and they've got them all lowercase, as does the innovator. Thus, these were left lowercase for consistency.

/S/ 3/4/96

David Konigstein Date
Primary Reviewer

/S/ 3-5-96

John Grace Date
Acting Team Leader, Labeling Review Branch

/S/ 6/96

cc: ANDA 74-664, Dup, Division File
see x:\new\firmsam\hitech\ltrs&rev\74664na2.1

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

Date of Review: March 1, 1996

ANDA Number: **74-664** Review Cycle: **2**

Dates of Submission:
- November 27, 1995 AC (Draft labels and labeling)
- November 27, 1995 AA (Side-by-side comparison)

Applicant's Name [as seen on 356(h)]: **Hi-Tech Pharmacal Co., Inc.**

Manufacturer's Name (If different than applicant): Same

Proprietary Name: None

Established Name: **Cimetidine Hydrochloride Oral Solution, 300 mg (base)/ 5 mL**

1° Reviewer: D.Konigstein

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE CHEMISTRY COMMENTS TO THE FIRM:

1. CONTAINER - 8 fl oz (237 mL) and 16 fl oz (473 mL)

   Revise the storage statement to read: Satisfactory in draft.

   Store at controlled room temperature 20-25°C (68-77°F) ~~[see USP]~~. OK. Keep.

2. INSERT

   a. DESCRIPTION

      i. ... cyano-*N*-methyl ... [cyano not italic, italic N].

      ii. Inactive Ingredients

         A). "flavor" [singular].

         B). "dibasic sodium phosphate anhydrous" rather than ~~[illegible]~~

      iii. We encourage inclusion of the pH range.

X:\ drive corrected DK 4/24/96

b. CLINICAL PHARMACOLOGY

i. Second paragraph, line 2 - Do not capitalize "cimetidine".

ii. Chemically Stimulated, Table - Please add sufficient spacing between the Stimulant Dose and Cimetidine columns. The "(iv)" on the Insulin line appears to be with the Cimetidine column.

iii. Pharmacokinetics, Duodenal Ulcer, Active Duodenal Ulcer - Capitalize the "U" in "ulcer" that is in the Table heading.

c. INDICATIONS AND USAGE

i. First sentence - We acknowledge an error in our August 4, 1995, letter which advised you to revise this to read "Cimetidine tablets are indicated in: ...". Please revise this sentence to read:

> Cimetidine Hydrochloride Oral Solution is indicated in: ...

ii. Short-term treatment of active duodenal ulcer, last sentence - insert "oral" before "cimetidine" in two locations.

d. PRECAUTIONS

i. General, second sentence - "rare" rather than

ii. Drug Interactions - Please insert a line space between paragraphs four and five.

iii. Pediatric Use - Use "pediatric patients" rather than ~~~~ in two locations.

e. ADVERSE REACTIONS

i. Hepatobiliary - Insert a line space between paragraphs one and two.

ii. Musculoskeletal - Do not capitalize "cimetidine".

iii. Integumental - ... Stevens-Johnson ... [spelling].

f. OVERDOSAGE

Third paragraph, last sentence - Delete excess space and do not capitalize "cimetidine" (two locations).

g. DOSAGE AND ADMINISTRATION

i. Duodenal Ulcer, Active Duodenal Ulcer

A). First paragraph

1). First sentence - ... healing (see Clinical Pharmacology-Antisecretory Activity-Acid Secretion).

2). Second sentence - ... trials (see Clinical Pharmacology-Clinical Trials-Duodenal Ulcer-Active Duodenal Ulcers). [note "trials" - spelling].

B). Second paragraph, line 1 - ... U.S. oral dose-ranging ...

C). Fifth paragraph - ... bedtime (see Clinical Pharmacology-Clinical Trials-Duodenal Ulcer-Active Duodenal Ulcers).

D). Seventh paragraph - ... for 4 to 6 weeks ... ["6" rather than ~~~].

ii. Active Benign Gastric Ulcer

A). Line 4 - ... treatment (see Clinical Pharmacology-Clinical Trials) ...

B). Line 7 - Do not capitalize "cimetidine".

iii. Dosage Adjustment for Patients with Impaired Renal Function

A). First sentence - Do not capitalize "cimetidine".

B). Use "every" rather than '~~~

h. HOW SUPPLIED

~~i.~~ ← Please use "8 fl oz" and "16 fl oz" rather than "eight oz" and "one pint".

~~ii. See comment under CONTAINER.~~

X-1 done corrected DC 9/11/96

Please revise your labels and labeling, as instructed above, and submit final printed labels and labeling. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
PROPRIETARY NAME			X
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X

Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring:			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration? See FTR - Bio	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement? See FTR	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			X
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			X
Insert labeling references a food effect or a no-effect? If so, was a food study done? Products are rated AA. Waiver granted. See FTR			

Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			X

FOR THE RECORD:

1. BASIS OF REVIEW:

The reference listed drug labeling is Tagamet® SmithKline Beecham; Revised July 1994; Approved February 22, 1995. This is confirmed by the MIS system. Labeling guidance; Revised September 1995; for Cimetidine Tablets was also utilized except for the DESCRIPTION section which was based on Cimetidine Hydrochloride Injection since the Oral Solution is the salt form.

2. PACKAGING CONFIGURATIONS:

RLD: 237 mL amber glass bottles
5 mL single-dose units, 10s
The innovator no longer has a [redacted] This was acknowledged in the approval letter for the current insert.

ANDA: The insert lists 237 mL and 473 mL available in amber PET with CRCs. Though on page 442 of original submission, the firm proposes the 8 fl oz size in both [redacted] and amber PET containers.

3. DISPENSING RECOMMENDATIONS

USP - Product is not a USP monograph.
ANDA - Dispense in a tight, light-resistant container as defined in the USP.
NDA - Dispense in a tight, light-resistant container.

4. STORAGE RECOMMENDATIONS

USP: Not a USP product.
NDA: Store between 15°-30°C (59°-86°)F.
ANDA: Store at CRT 15°-30°C (59°-86°F).

Per 11-16-95 Memo titled Uniform Storage Statements in Drug Substance and Drug Product Labeling, authored by Dr. Poochikian, Chairman of the CDER Stability Committee, the comment was made to revise the storage statement to "Store at controlled room temperature 20-25°C (68-77°F) [see USP]."

5. INACTIVE INGREDIENTS/ BIOEQUIVALENCY ISSUES: The formulations are slightly different. See Bio waiver

granted 11-4-95 listing comparison against RLD for ingredients.

6. PATENT/EXCLUSIVITY ISSUES: No patents or exclusivities exist for Cimetidine Hydrochloride Oral Solution.

7. ALCOHOL

Per composition statement, 0.15 mL of Alcohol USP per 5 mL which equals 0.03 mL alcohol contained in 1 mL.

A little over [redacted] claimed.

8. Regarding DOSAGE AND ADMINISTRATION comments - It was noted the innovator's labeling did not expand the references to other sections entirely. These comments reflect the actual section/subsection(s) headings. Usually, we prefer to have the section headings capitalized in such references, however the comment wasn't made in review one and they've got them all lowercase, as does the innovator. Thus, these were left lowercase for consistency.

/S/ 3/4/96

David Konigstein Date
Primary Reviewer

/S/ 3-5-96

John Grace Date
Acting Team Leader, Labeling Review Branch

/S/ 3/6/96

cc: ANDA 74-664, Dup, Division File
see x:\new\firmsam\hitech\ltrs&rev\74664na2.1

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

Date of Review: July 23, 1996

ANDA Number: 74-664 Review Cycle: 3

Dates of Submission: June 12, 1996 [FPL]
Applicant's Name [as seen on 356(h)]: Hi-Tech Pharmacal Co., Inc.

Manufacturer's Name (If different than applicant): Same
Proprietary Name: None

Established Name: Cimetidine Hydrochloride Oral Solution, 300 mg (base)/ 5 mL

1° Reviewer: Jacqueline White, Pharm.D.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes
If no, list why:

Container Labels: Satisfactory in FPL as of June 12, 1996 submission; 8 fl.oz & 16 fl.oz.

Carton Labeling: n/a

Unit Dose Blister Label: n/a

Unit Dose Carton Label: n/a

Professional Package Insert Labeling: Satisfactory in FPL as June 12, 1996 submission.

Patient Package Insert Labeling: n/a

Auxiliary Labeling: n/a

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Tagamet

=NDA Number:

NDA Drug Name: Cimetidine Hydrochloride oral solution

NDA Firm: SmithKline Beecham

=Date of Approval of NDA Insert and supplement #:

=Has this been verified by the MIS system for the NDA?
Yes No

=Was this approval based upon an OGD labeling guidance?
Yes No

If yes, give date of labeling guidance:

Basis of Approval for the Container Labels:

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
PROPRIETARY NAME			X
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
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Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	

Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring:			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
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Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
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Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
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Insert labeling references a food effect or a no-effect? If so, was a food study done? Products are rated AA. Waiver granted. See FTR			
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			X

FOR THE RECORD:

[From previous reviews/reviewer]

1. BASIS OF REVIEW:

The reference listed drug labeling is Tagamet® SmithKline Beecham; Revised July 1994; Approved February 22, 1995. This is confirmed by the MIS system. Labeling guidance; Revised September 1995; for Cimetidine Tablets was also utilized except for the DESCRIPTION section which was based on Cimetidine Hydrochloride Injection since the Oral Solution is the salt form.

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9. The following question was under the NOTE TO THE CHEMIST from a previous review/reviewer.

Is [redacted]

The chemist written response was: [redacted]
called [redacted]
The firm still has listed [redacted]
[redacted] as an inactive ingredients and not

Page 102 lists [redacted] a component.
KB.

4/24/97
Confirmed with chemist who is satisfied the two are the same ingredient. USP/NF monograph was helpful.
/S/ KLO
AJC

10. The description of the finished dosage form in the HOW SUPPLIED section is consistent with the finished product specs found on page 498 in Vol. 1.2.

/S/ J. White 7/25/96

Primary Reviewer Date

/S/ 7/25/96

Acting Team Leader, Date
Labeling Review Branch

cc: ANDA 74-664
Division File
HFD-613/JWhite/AVezza(no cc:)
njg/7/25/96/x:\new\firmsam\hitech\ltrs&rev\74664ap.1
Review

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION

DATE: September 16, 1996

PRODUCT NAME: Cimetidine Hydrochloride Oral Solution

ANDA/AADA NUMBER: 74-664

FIRM NAME: HiTech Laboratories, Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: JoAnn Curry
Elan Bar-giora
Dr. Haiao

PARTICIPANT(S) TELEPHONE: (516) 789-8228

MINUTES OF CONVERSATION:

Returned Ms. Curry's call regarding clarification of questions 1 and 4 of our August 30, 1996 deficiency letter. They implied that they had made the change in the ——— specifications requested in a previous submission dated 11/27/95. I pointed out to them that the agreed upon change in the specifications was not reflected in their submission dated 6/12/96. While on the phone, they looked through the submission and acknowledged that in fact the change is specifications had not been done and they apologized.

As for #4, the requested data comparing their product with the innovator's had been collected, but they had failed to submit the data. They said they would submit the data as requested.

They thanked me and again apologized.

/S/

NAME OF OGD REPRESENTATIVE: Brenda T. Arnwine

SIGNATURE OF OGD REPRESENTATIVE:

DIVISION/BRANCH: Div Chem II/Br 6

DIVISION REVIEW SUMMARY

ANDA: 74-664

FIRM: Hi-Tech Pharmacal Co., Inc.

DOSAGE FORM: Oral Solution STRENGTH: 300 mg(base)/5 mL

DRUG: Cimetidine

CGMP STATEMENT/EIR UPDATE STATUS: Pending

BIO STUDY INFORMATION: Bio-waiver granted 11/4/95.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S)

Acceptable 6/16/97.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? yes

The containers used in the stability study are of the same size and material (8 oz. [redacted] and PET and 16 oz. PET) as described in the container section. The firm submitted accelerated stability data for the product packaged in the all container sizes.

The firm requests an expiration date of 24 months based on the data submitted.

The stability tests and specifications are indicated in the following table:

TEST	SPECIFICATION
Description	Yellow orange flavored liquid
Assay (cimetidine)	[redacted]
Assay [redacted]	[redacted]
Assay [redacted]	[redacted]
Alcohol	[redacted]
pH	5.1-[redacted]
[redacted]	NMT [redacted]

Impurities/Degradants [ ] Total	NMT —% NMT —% NMT —% NMT —%

LABELING: See approval summary by J. White dated 7/23/96.

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?)

No information on bio-batch since a waiver was granted.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

The firm manufactured a ——— stability batch. The — rule was met.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

The intended production batch size is ———

RECOMMENDATION: Approvable.

SIGNATURE: /S/ DATE: 5/2/97

/ V

Finished Product Specification Testing

The following tests will be performed:

Test	Specification
Description	yellow, orange flavor liquid
Identification	[redacted]
pH	5.1 - 5.7
[redacted]	[redacted]
[redacted]	[redacted]
Assay	[redacted]
Alcohol	[redacted]
[redacted]	[redacted]
[redacted]	Total LT [redacted]
[redacted]	None
[redacted]	None
[redacted]	None
[redacted]	None
Impurities/Degradants	
Individual unknowns	NMT [redacted]%
[redacted]	NMT [redacted]%
[redacted]	NMT [redacted]%
[redacted]	NMT [redacted]%
Total	NMT [redacted]%

CDER Establishment Evaluation Report
for October 22, 1997

Application: **ANDA 74664/000**
Stamp: **01-MAY-1995** Regulatory Due:
Applicant: **HI TECH**
369 BAYVIEW AVE
AMITYVILLE, NY 11701

Priority:
Org Code: **600**
Action Goal:
District Goal: **01-JUL-1996**
Brand Name:
Established Name: **CIMETIDINE HYDROCHLORIDE**
Generic Name:
Dosage Form: **SOL (SOLUTION)**
Strength: **300 MG/ 5 ML**

FDA Contacts: **K. BERNARD (HFD-640) 301-827-5849 , Review Chemist**

Overall Recommendation:

ACCEPTABLE on 22-OCT-1997 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: **2433247**
HI TECH PHARMACAL CO INC
369 BAYVIEW AVE
AMITYVILLE, NY 11701

DMF No:

AADA No:

Profile: **LIQ** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 31-JAN-1996**
Decision: **ACCEPTABLE**
Reason:

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **DO RECOMMENDAT 22-OCT-1997**
Decision: **ACCEPTABLE**
Reason: **ADEQUATE FIRM RESPONSE**

Establishment: [redacted]

DMF No:

AADA No:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 07-JUL-1995**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:

AADA No:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDAT 07-JUL-1995**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

CDER Establishment Evaluation Report
for October 22, 1997

Establishment: [redacted]

DMF No:

AADA No:

Profile: NEC OAI Status: NONE

Last Milestone: OC RECOMMENDAT 22-OCT-1997

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Responsibilities: [redacted]

Establishment: [redacted]

DMF No: 10982 9459

AADA No:

Profile: CSN OAI Status: NONE

Last Milestone: OC RECOMMENDAT 29-SEP-1997

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Responsibilities: [redacted]

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-664

CORRESPONDENCE

HI-TECH PHARMACAL CO., INC.

369 BAYVIEW AVENUE, AMITYVILLE, N.Y.11701
(516) 789-8228

April 3, 1997

AMENDMENT
N/AM

Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

Re: Telephone Amendment to Pending ANDA
Product: Cimetidine Hydrochloride Oral Solution
ANDA 74-664

Dear Sir:

Reference is made to the above abbreviated new drug application and our telephone conversation of April 3, 1997 with Mr. Andrew Langowski.

Submitted herewith is the following information:

1. Finished product specifications with the total impurities set at NMT [redacted] and stability specifications with the total impurities set at NMT [redacted]

2. [redacted] (from the February 19, 1997 minor amendment) labeled to indicate where the [redacted]

If you have any questions concerning the submitted information, please feel free to call Elan Bar-Giora at 516-789-8228.

Sincerely,

HI-TECH PHARMACAL CO., INC.

Elan Bar-Giora
Executive Vice President

EB:jc
Enc.

RECEIVED
APR 07 1997
GENERIC DRUGS

noted
jrs 2/26/97

HI-TECH PHARMACAL CO., INC.

369 BAYVIEW AVENUE, AMITYVILLE, N.Y.11701
(516) 789-8228

February 19, 1997

ORIG AMENDMENT
N/AM

Frank O. Holcombe, Jr., Ph.D.
Director, Div. of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

MINOR AMENDMENT

Re: Minor Amendment to Pending ANDA
Product: Cimetidine Hydrochloride Oral Solution
ANDA 74-664

Dear Dr. Holcombe:

Reference is made to the above abbreviated new drug application dated April 28, 1995, our amendment dated September 17, 1996 and your letter dated October 18, 1996.

Submitted herewith is our response to your comments.

If you have any questions concerning the submitted information, please feel free to call Elan Bar-Giora at 516-789-8228.

Sincerely,

HI-TECH PHARMACAL CO., INC.

Elan Bar-Giora

Elan Bar-Giora
Executive Vice President

EB:jc
Enc.

RECEIVED
FEB 21 1997
GENERIC DRUGS

2-24-97 Madhu

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

DATE: Oct 22, 1996

TO: Hi-Tech Pharmacal Co. Inc. FROM: Kasundra Sherrod

Attn: Ela Bar-Dina Project Manager

PHONE: 516-789-8228 PHONE: (301) 594-1300

FAX: (516) 789-8429 FAX: (301) 594-0180

NUMBER OF PAGES: 2
(Excluding Cover Sheet)

With this facsimile, the Office of Generic Drugs is providing you with a copy of a not approvable letter requesting your response in the form of a MINOR AMENDMENT for the following abbreviated new drug/antibiotic application:

(ANDA)/AADA NUMBER: 74664 DATE OF LETTER: 10/18/96

NAME OF DRUG PRODUCT: Cimetidine Hydrochloride Oral Solution, 300 mg (base)/5 mL

SPECIAL INSTRUCTIONS:

faxed 10/22/96
2:40

ANDA 74-664

Hi-Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

OCT 18 1996

Dear Sir:

This is in reference to your abbreviated new drug application dated April 28, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cimetidine Hydrochloride Oral Solution, 300 mg (base)/5 mL.

Reference is also made to your amendment dated September 17, 1996.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

1. It was noted that you have proposed the use of your assay method (#281) for cimetidine to quantitate impurities/degradants. The method is not suitable since the detector monitors the [redacted] Impurities/degradants should be monitored at between [redacted] This is probably the reason you are not detecting any degradants. We request that you develop and validate a method with the detector set somewhere within the range of [redacted]

2. Additional work should be done to identify and evaluate impurity levels in the subject drug product. We request that you obtain commercially available standards for the [redacted] degradation products of cimetidine. Please evaluate the subject drug product for the presence of these degradants and provide [redacted] to show the elution times of these components.

3. It was also noted that your calculation for degradants is not appropriate since peak area normalization is being used as the technique for quantitation. We request that you use the external standard technique.

If you choose not to use the impurity standards for quantitation, then the peak responses for the impurities should be compared to that obtained for a known amount of active ingredient (i.e., ——) of label claim. Please revise the calculation to indicate that the response for any single impurity is not more than that obtained for the —— standard. The sum total of the area count responses for the degradants should not be more than —— that obtained for the —— standard.

4. We request that you calculate the degradant levels in stability samples stored at room temperature using the requested quantitation technique. Please submit the results for review.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/s/ 10/16/96

Frank Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

HI-TECH PHARMACAL CO., INC.

369 BAYVIEW AVENUE, AMITYVILLE, N.Y.11701
(516) 789-8228

noted KLS
9/25/96

September 17, 1996

Frank O. Holcombe, Jr., Ph.D.
Director, Div. of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

AMENDMENT
MINOR AMENDMENT
N/AM

Re: Minor Amendment to Pending ANDA
Product: Cimetidine Hydrochloride Oral Solution
ANDA 74-664

Dear Dr. Holcombe:

Reference is made to the above abbreviated new drug application, our amendment dated June 12, 1995, our amendment dated June 12, 1996 and your letter dated August 30, 1996.

Submitted herewith is our response to your comments.

If you have any questions concerning the submitted information, please feel free to call Elan Bar-Giora at 516-789-8228.

Sincerely,

HI-TECH PHARMACAL CO., INC.

Elan Bar-Giora

Elan Bar-Giora
Executive Vice President

EB:jc
Enc.

RECEIVED
SEP 18 1996
GENERIC DRUGS

ANDA 74-664

Hi-Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

AUG 30 1996

Dear Sir:

This is in reference to your abbreviated new drug application dated April 28, 1995, and your amendment dated June 12, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cimetidine Hydrochloride Oral Solution, 300 mg (base)/5 mL.

Reference is also made to your amendment dated June 12, 1996.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

1. Although the revised batch records that were submitted in the 6/12/96 amendment include an in-process test for alcohol, it is noted, that the [redacted] specification limits are listed as [redacted] You had previously agreed to tighten these limits to [redacted] as requested. You should re-revise these records and resubmit them with the correct information and provide assurance that you have adopted the revised specification limits.

2. The revised stability protocol that you submitted did

[redacted]

3. [redacted]

4. Due to the difficulty that you have experienced regarding the use of a impurities/degradation test with reasonable specification limits for Cimetidine Hydrochloride Solution, we recommend that you run 1 or 2 lots of innovator drug product as a standard (under similar conditions) and determine if the impurities/degradation levels are comparable with your own product utilizing your impurities/degradation method.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 8/30/96

Frank O. Holcombe, Jr. Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

HI-TECH PHARMACAL CO., INC.

369 BAYVIEW AVENUE, AMITYVILLE, N.Y.11701
(516) 789-8228

June 12, 1996

Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

Re: Major Amendment to Pending ANDA
Product: Cimetidine Hydrochloride Oral Solution 300 mg (base) 5 mL
ANDA 74-664

Dear Sir:

Reference is made to the above abbreviated new drug application submitted on April 28, 1995, our amendment dated November 27, 1995 and your letter dated April 30, 1996.

Submitted herewith is our response to your comments.

If you have any questions concerning the submitted information, please feel free to call Elan Bar-Giora at 516-789-8228.

Sincerely,

HI-TECH PHARMACAL CO., INC.

Elan Bar-Giora
Executive Vice President

EB:jc
Enc.

ANDA 74-664

Hi-Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

APR 30 ...

Dear Sir:

This is in reference to your abbreviated new drug application dated April 28, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cimetidine Hydrochloride Oral Solution, 300 mg (base)/5 mL.

Reference is also made to your amendment dated November 27, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. [redacted]

2. [redacted]

3. [redacted] rd

4. We note that you have included a packaging [redacted]

Redacted 1

pages of trade secret and/or confidential commercial information

2. INSERT

a. DESCRIPTION

i. ... cyano-*N*-methyl ... [cyano not italic, italic N].

ii. Inactive Ingredients

A). "flavor" [singular].

B). "dibasic sodium phosphate anhydrous" rather than ~~~~

iii. We encourage inclusion of the pH range.

b. CLINICAL PHARMACOLOGY

i. Second paragraph, line 2 - Do not capitalize "cimetidine".

ii. Chemically Stimulated, Table - Please add sufficient spacing between the Stimulant Dose and Cimetidine columns. The "(iv)" on the Insulin line appears to be with the Cimetidine column.

iii. Pharmacokinetics, Duodenal Ulcer, Active Duodenal Ulcer - Capitalize the "U" in "ulcer" that is in the Table heading.

c. INDICATIONS AND USAGE

i. First sentence - We acknowledge an error in our August 4, 1995, letter which advised you to revise this to read "Cimetidine tablets are indicated in: ...". Please revise this sentence to read:

Cimetidine Hydrochloride Oral Solution is indicated in: ...

ii. Short-term treatment of active duodenal ulcer, last sentence - insert "oral" before "cimetidine" in two locations.

d. PRECAUTIONS

i. General, second sentence - "rare" rather than " ~~~~

ii. Drug Interactions - Please insert a line space between paragraphs four and five.

iii. Pediatric Use - Use "pediatric patients" rather than ~~~~ in two locations.

e. ADVERSE REACTIONS

i. Hepatobiliary - Insert a line space between paragraphs one and two.

ii. Musculoskeletal - Do not capitalize "cimetidine".

iii. Integumental - ... Stevens-Johnson ... [spelling].

f. OVERDOSAGE

Third paragraph, last sentence - Delete excess space and do not capitalize "cimetidine" (two locations).

g. DOSAGE AND ADMINISTRATION

i. Duodenal Ulcer, Active Duodenal Ulcer

A). First paragraph

1). First sentence - ... healing (see Clinical Pharmacology-Antisecretory Activity-Acid Secretion).

2). Second sentence - ... trials (see Clinical Pharmacology-Clinical Trials-Duodenal Ulcer-Active Duodenal Ulcers). [note "trials" - spelling].

B). Second paragraph, line 1 - ... U.S. oral dose-ranging ...

C). Fifth paragraph - ... bedtime (see Clinical Pharmacology-Clinical Trials-Duodenal Ulcer-Active Duodenal Ulcers).

D). Seventh paragraph - ... for 4 to 6 weeks ... ["6" rather than ~~~

ii. Active Benign Gastric Ulcer

A). Line 4 - ... treatment (see Clinical Pharmacology-Clinical Trials) ...

B). Line 7 - Do not capitalize "cimetidine".

iii. Dosage Adjustment for Patients with Impaired Renal Function

A). First sentence - Do not capitalize "cimetidine".

B). Use "every" rather than ——

h. HOW SUPPLIED

Please use "8 fl oz" and "16 fl oz" rather than ——

Please revise your labels and labeling, as instructed above, and submit final printed labels and labeling. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 4/30/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

HI-TECH PHARMACAL CO., INC.

369 BAYVIEW AVENUE, AMITYVILLE, N.Y.11701
(516) 789-8228

November 27, 1995

AMENDMENT
MAA

Charles Ganley, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

RE: Cimetidine Hydrochloride Oral Solution, 300 mg (base)/5 mL
ANDA 74-664

Dear Sir:

Enclosed please find a side-by-side comparison of our proposed labeling (container labels and package insert) with the approved labeling for the reference listed drug with all differences annotated and explained.

Additionally, we are enclosing an additional copy of the analytical methods.

Sincerely,

HI-TECH PHARMACAL CO., INC.

Elan Bar-Giora

Elan Bar-Giora
Executive Vice President

EB:jc
Enc.

RECEIVED
NOV 29 1995
GENERIC DRUGS

Madeline 12-1-95

Labeling Review Completed 3-1-96 DiCompt

HI-TECH PHARMACAL CO., INC.

369 BAYVIEW AVENUE, AMITYVILLE, N.Y.11701
(516) 789-8228

November 27, 1995

NDA ORIG AMENDMENT

N/A C

Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

Re: Major Amendment to Pending ANDA
Product: Cimetidine Hydrochloride Oral Solution, 300 mg/5 mL
ANDA 74-664

Dear Sir:

Reference is made to our abbreviated new drug application dated April 28, 1995 and your communication of August 4, 1995.

Submitted herewith is our response to your comments.

If you have any questions concerning the submitted information, please feel free to call Elan Bar-Giora at 516-789-8228.

Sincerely,

HI-TECH PHARMACAL CO., INC.

Elan Bar-Giora
Executive Vice President

EB:jc
Enc.

RECEIVED

NOV 29 1995

GENERIC DRUGS

Amend 12-1-95

ANDA 74-664

NOV 17 1995

Hi-Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

Dear Sir:

Reference is made to your abbreviated new drug application dated April 28, 1995, submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Cimetidine Hydrochloride Oral Solution 300 mg/5 mL (eq. base).

The following comments pertain **only** to the bioequivalency issues in the April 28, 1995 submission.

> The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-664

Hi-Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

AUG 4 1995

Dear Sir:

This is in reference to your abbreviated new drug application dated April 28, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cimetidine Hydrochloride Oral Solution, 300 mg (base)/5 mL.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. Please revise your composition statement to include compendial designations where applicable.

2. [redacted]

3. [redacted]

4. In accordance with USP 23, Supplement 1, you are requested to add USP test <467> for Organic Volatile Impurities to the Certificate of Analysis for Cimetidine, USP.

5. With regard to the lot numbers listed on the Certificates of Analysis included in the application, it is confusing in many instances what the actual lot numbers are for your vendors, as well as those included on your own COA's. For example, page 164 includes lot number listing 049-3E on the certificate, yet there is a handwritten lot number 93-D-20 at the top of the certificate. Please make this information clearer.

6. All [redacted] Certificates of Analysis (both vendor and your own) should include USP or NF designations when appropriate.

Redacted 3

pages of trade secret and/or confidential commercial information

2. Place an asterisk following the expression of strength and immediately before the "Each 5 mL contains..." statement as follows:

300 mg/5 mL*

*Each 5 mL (1 teaspoonful) contains...

INSERT:

1. GENERAL COMMENTS

   a. Ensure that the "number" and the "unit of expression of strength" appear on the same line. [i.e., 800 mg, 1600 mg, etc.] Correct throughout the text of the insert.

   b. Please revise the insert so that you have consistent spacing between the section headings, subsection headings and sub-subsection headings and the text of the insert.

   c. Please revise the phrase "cimetidine treated" throughout the insert, so that there is a hyphen between the two words.

2. TITLE

   See comment 1 under CONTAINER.

3. DESCRIPTION

   a. Revise the chemical name as follows:

      ...cyano-*N*-methyl...1*H*...

   b. Revise paragraph 2 to read as follows:

      The molecular formula for cimetidine hydrochloride is $C_{10}H_{16}N_6S \bullet HCl$ and the molecular weight is 288.80. The structural formula of cimetidine hydrochloride is:

   c. Revise the chemical structure to be cimetidine hydrochloride.

   d. Delete paragraph 4

   e. Solubility Characteristics - Delete the first sentence.

f. Delete the title "[redacted]" and revise the paragraph to read as follows:

Each 5 mL (1 teaspoonful), for oral administration, contains cimetidine hydrochloride...2.8%. In addition, the oral solution contains the following inactive ingredients:...

g. Inactive ingredients

We note you have not included hydrochloric acid in your listing of inactive ingredients. We note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance). We believe this is an important public health measure. Please respond accordingly by correctly noting all the inactive ingredients present in this product. If you elect not to mention an inactive ingredient because it is a trade secret, you should use the phrase "and other ingredients", and provide supporting data concerning the "trade secret".

4. CLINICAL PHARMACOLOGY

a. Antisecretory Activity, Chemically Stimulated Table

i. Correct the spelling of "Pentagastrin".

ii. Insert a space between the "number" and the "unit of expression of strength" throughout the text of the table. [i.e., 1.5 mg/kg]

iii. Insert a space between "%" and "Inhibition".

b. Chemically Stimulated - Delete the last paragraph. This information pertains to the intravenous dosage form only.

c. Pharmacokinetics - Delete paragraph 2 and the last sentence of paragraph 3. This information pertains to the intravenous dosage form only.

d. CLINICAL TRIALS - This is a subsection under CLINICAL PHARMACOLOGY. Please revise so that the title does not have the same prominence as section headings.

e. Active Duodenal Ulcer

i. Capitalize the "U" in "ulcer" that is in the sub-subsection title and in the Table heading.

ii. Insert "oral" in the following places:

(a) Paragraph 1, line 3 - ...with oral cimetidine...

(b) Table heading - ...Various Oral Cimetidine...

iii. Column one heading - "Regimen" rather than "Regiment".

f. Maintenace Therapy in Duodenal Ulcer

i. Delete the bold print from the subsubsection heading to be consistent with other subsubsection headings throughout the insert.

ii. Last sentence - Insert a space between "400" and "mg".

g. Active Benign Gastric Ulcer, last paragraph - Delete the italics from "cimetidine".

h. Gastroesophageal Reflux Disease

i. Delete the italics from "cimetidine" in paragraphs 1 and 3.

ii. Table - Insert a blank line/space between the information in trial 1 and 2.

i. Delete the subsection [redacted]

j. Pathological Hypersecretory Conditions - Delete the italics from "cimetidine". [2 places]

5. INDICATIONS AND USAGE

a. Revise the first sentence to read:

Cimetidine tablets are indicated in:...

b. [redacted]

c. [redacted]

6. PRECAUTIONS

a. General

i. Delete paragraph 1. This information pertains to the intravenous dosage form only.

ii. Paragraph 3, line 5 - ...states have...

b. Drug Interactions

i. Paragraph 3, line 3 - Revise to read:

...theophylline extended-release tablets demonstrated...

ii. Insert the following text as the penultimate paragraph:

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.

c. Insert the following text to appear as the last subsection:

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.

7. ADVERSE REACTIONS

Insert the following text to appear as the last subsection:

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

8. DOSAGE AND ADMINISTRATION

a. Active Duodenal Ulcer

i. Paragraph 4 - Delete the [redacted] in "1 cm".

ii. Delete the space between paragraph 5 and 6. This should be one paragraph.

iii. Insert a space/blank line between paragraphs 7 and 8.

b. Active Benign Gastric Ulcer - Capitalize the "G" in "Gastric".

c. Delete the subsection [redacted].

d. Pathological Hypersecretory Conditions

i. Capitalize the "E" in "Ellison and the "S" in "Syndrome".

ii. Third line - ... "doses" ... (spelling).

e. Delete the subsection '[redacted]'.

f. Dosage Adjustment for Patients with Impaired Renal Function - Delete the last paragraph of this subsection.

9. HOW SUPPLIED

a. Second line

...containing 300 mg of cimetidine per...

b. Revise the storage temperature to read as follows:

...15° to 30°C (59° to 86°F).

Please revise your container labels and package insert labeling, then prepare and submit draft container labels and insert labeling for review and comment.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 8/4/95

Florence S. Fang
Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-664

Hi-Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

JUN 2 1995

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Cimetidine Hydrochloride Oral Solution, 300 mg (base)/5 mL

DATE OF APPLICATION: April 28, 1995

DATE OF RECEIPT: May 1, 1995

We will correspond with you further after we have had the opportunity to review the application.

However, you have failed to include a side-by-side comparison of your proposed labeling (container labels and package insert) with the approved labeling for the reference listed drug with all differences annotated and explained [314.94(a)(8)(iv)]. Please provide this comparison.

Also, in the interim, please submit one additional copy of the analytical methods and descriptive information needed to perform the tests on the samples (both the —— active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

If the above methodology is not submitted, the review of the application will be delayed.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Consumer Safety Officer
(301) 594-1300

Sincerely yours,

/S/ 6/2/95

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-664
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Acting Chief /S/ date
HFD-615/WRussell, C[illegible] /S/ 5/15/95 date
HFD-645/BArnwine, Sup Chemist /S/ date 5/24/95
HFD-610/JPhillips, Chief LRB /S/ date
WP File\russell\74\74-656
F/T by Fox 5/12/95
ANDA Acknowledgement Letter!

HI-TECH PHARMACAL CO., INC.

369 BAYVIEW AVENUE, AMITYVILLE N.Y.11701
(516) 789-8228

April 28, 1995

Director
Office of Generic Drugs
Center for Drug Evaluation & Research
FOOD & DRUG ADMINISTRATION
Metro Park North II
HFD-600, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: CIMETIDINE HYDROCHLORIDE ORAL SOLUTION, 300 mg/5 mL

Dear Sir:

Pursuant to 21 CFR part 314.92, subpart C and Section 505(j) of the Federal Food, Drug and Cosmetic Act, we are submitting an Abbreviated New Drug Application for Cimetidine Hydrochloride Oral Solution. This submission contains an archival copy (two volumes) and a review copy (two volumes) and a method validation package.

The product is an oral solution which contains an active ingredient in the same strength and dosage form as the reference listed drug, Tagamet Solution (Smith Kline Beecham's NDA 17-924). The formulation of Hi-Tech's product

The labeling of the new drug is the same as that of Tagamet except for changes that are necessary due to a change in the manufacturer and the above listed ingredient difference.

Following this cover letter, please find the Certification required by the Generic Drug Enforcement Act of 1992, and the Office of Generic Drugs letter dated January 15, 1993 and our certification that a true copy of this application has been submitted to the New York District Office. The required patent certification information to show that the drug product provided in this application is the same as the listed drug and a completed Form FDA 356h are also included.

If you have any questions concerning this ANDA, please contact Elan Bar-Giora at 516-789-8228. We look forward to your prompt review of the submitted information.

Sincerely,

HI-TECH PHARMACAL CO., INC.

Elan Bar-Giora
Executive Vice President

Enc.

RECEIVED

MAY 0 1 1995

GENERIC DRUGS