74467

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

74467

Trade Name:

Generic Name: Ranitidine Tablets USP, 150 mg and 300 mg. (present as the hydrochloride).

Sponsor: Geneva Pharmaceuticals, Inc.

Approval Date: August 29, 1977

Indications: See Label.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
74467

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74467

APPROVAL LETTER

ANDA 74-467

AUG 29 1997

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2655 W. Midway Blvd.
P.O. Box 466
Broomfield, CO 80038-0446

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated February 16, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ranitidine Tablets USP, 150 mg and 300 mg (present as the hydrochloride).

Reference is also made to your amendments dated March 13, April 24, August 27, and August 28, 1997.

The listed drug product referenced in your application is subject to a period of patent protection which expires June 4, 2002, (patent 4,521,431). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of ranitidine hydrochloride will not infringe on the patent or that the patent is otherwise invalid. You further informed the Agency that Glaxo, Inc. initiated a patent infringement suit against you in the United States District Court for the District of New Jersey (Glaxo Inc., Glaxo Group Limited, and Allen & Hanburys Limited v. Geneva Pharmaceuticals Inc., Ciba-Geigy Corporation, Interchem Trading Corporation and Union Quimico Farmaceutica S.A., Civil Action Nos. 94-1921 and 94-4589.) You also have notified the Agency that the case was dismissed with prejudice on August 6, 1997.

The Agency also recognizes that the 30-month period identified in Section 505(j)(4)(B)(iii) of the Act, during which time FDA was precluded from approving your application, expired prior to the August 6, 1997 decision of the court.

The Agency has reviewed the application of the 180-day exclusivity provisions of the Act in reference to the ANDAs submitted for ranitidine hydrochloride tablets, and has concluded that Genpharm, Inc., as the first ANDA applicant to submit a

Paragraph IV Certification to the patent listed for the referenced drug, received the right to the 180-days of exclusivity. This period of exclusivity expires on August 29, 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 Ranitidine Tablets USP, 150 mg and 300 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zantac Tablets, 150 mg and 300 mg, respectively, of Glaxo Wellcome, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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:

74467

DRAFT FINAL PRINTED LABELING

7162

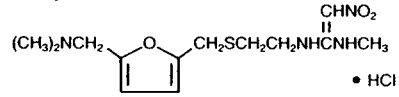
RANITIDINE TABLETS, USP

7162-6

MAY 29 1997

DESCRIPTION: Ranitidine hydrochloride is a histamine H_2-receptor antagonist. Chemically it is *N*-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-*N'*-methyl-2-nitro-1,1-ethenediamine, hydrochloride.

Ranitidine HCl is a white to pale yellow, crystalline substance that is very soluble in water. It has a slightly bitter taste and sulfur-like odor. It has the following structural formula:



$C_{13}H_{22}N_4O_3S \bullet HCl$ M.W. 350.87

Each tablet, for oral administration contains 168 mg or 336 mg ranitidine hydrochloride equivalent to 150 mg and 300 mg ranitidine, respectively. Inactive ingredients: D & C Red #30 Aluminum Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide. The **300 mg** also contains: D & C Yellow #10 Aluminum Lake.

CLINICAL PHARMACOLOGY: Ranitidine is a competitive, reversible inhibitor of the action of histamine at the histamine H_2-receptors, including receptors on the gastric cells. Ranitidine does not lower serum Ca^{++} in hypercalcemic states. Ranitidine is not an anticholinergic agent.

Antisecretory Activity:

1. *Effects on Acid Secretion:* Ranitidine inhibits both daytime and nocturnal basal gastric acid secretions as well as gastric acid secretion stimulated by food, betazole, and pentagastrin, as shown in the following table:

Effect of Oral Ranitidine on Gastric Acid Secretion

	Time after Dose, h	% Inhibition of Gastric Acid Output by Dose, mg			
		75-80	100	150	200
Basal	Up to 4		99	95	
Nocturnal	Up to 13	95	96	92	
Betazole	Up to 3		97	99	
Pentagastrin	Up to 5	58	72	72	80
Meal	Up to 3		73	79	95

It appears that basal-, nocturnal-, and betazole-stimulated secretions are most sensitive to inhibition by ranitidine, responding almost completely to doses of 100 mg or less, while pentagastrin- and food-stimulated secretions are more difficult to suppress.

2. *Effects on Other Gastrointestinal Secretions:*

Pepsin: Oral ranitidine does not affect pepsin secretion. Total pepsin output is reduced in proportion to the decrease in volume of gastric juice.

Intrinsic Factor: Oral ranitidine has no significant effect on pentagastrin-stimulated intrinsic factor secretion.

Serum Gastrin: Ranitidine has little or no effect on fasting or postprandial serum gastrin.

Other Pharmacologic Actions:

a. Gastric bacterial flora — increase in nitrate-reducing organisms, significance not known.

b. Prolactin levels — no effect in recommended oral or IV dosage, but small, transient, dose-related increases in serum prolactin have been reported after IV bolus injections of 100 mg or more.

c. Other pituitary hormones — no effect on serum gonadotropins, TSH, or GH. Possible impairment of vasopressin release.

d. No change in cortisol, aldosterone, androgen, or estrogen levels.

e. No antiandrogenic action.

f. No effect on count, motility, or morphology of sperm.

Pharmacokinetics: Ranitidine is 50% absorbed after oral administration, compared to an IV injection with mean peak levels of 440 to 545 ng/mL occurring at 2 to 3 hours after a 150 mg dose. The elimination half-life is 2.5 to 3 hours.

Absorption is not significantly impaired by the administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ranitidine, probably by delaying gastric emptying and transit time. In one study, simultaneous administration of high-potency antacid (150 mmol) in fasting subjects has been reported to decrease the absorption of ranitidine.

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94 ng/mL. Following a single oral dose of 150 mg, serum concentrations of ranitidine are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 mL/min, indicating active tubular excretion. Four patients with clinically significant renal function impairment (creatinine clearance 25 to 35 mL/min) administered 50 mg of ranitidine intravenously had an average plasma half-life of 4.8 hours, a ranitidine clearance of 29 mL/min, and a volume of distribution of 1.76 L/kg. In general, these parameters appear to be altered in proportion to creatinine clearance (see DOSAGE AND ADMINISTRATION).

In man, the N-oxide is the principal metabolite in the urine; however, this amounts to less than 4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool. Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant, alterations in ranitidine half-life, distribution, clearance, and bioavailability.

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Clinical Trials:

Active Duodenal Ulcer: In a multicenter, double-blind, controlled, US study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the patients treated with ranitidine as shown in the following table:

...of ... ition.

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 mL/min, indicating active tubular excretion. Four patients with clinically significant renal function impairment (creatinine clearance 25 to 35 mL/min) administered 50 mg of ranitidine intravenously had an average plasma half-life of 4.8 hours, a ranitidine clearance of 29 mL/min, and a volume of distribution of 1.76 L/kg. In general, these parameters appear to be altered in proportion to creatinine clearance (see DOSAGE AND ADMINISTRATION).

In man, the N-oxide is the principal metabolite in the urine; however, this amounts to less than 4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool. Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant, alterations in ranitidine half-life, distribution, clearance, and bioavailability.

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Clinical Trials:

Active Duodenal Ulcer: In a multicenter, double-blind, controlled, US study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the patients treated with ranitidine as shown in the following table:

	Ranitidine*		Placebo*	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	195	69/182 (38%)†	188	31/164 (19%)
Week 4		137/187 (73%)†		76/168 (45%)

*All patients were permitted p.r.n. antacids for relief of pain.
†$p < 0.0001$.

In these studies patients treated with ranitidine reported a reduction in both daytime and nocturnal pain, and they also consumed less antacid than the placebo-treated patients.

Mean Daily Doses of Antacid

	Ulcer Healed	Ulcer Not Healed
Ranitidine	0.06	0.71
Placebo	0.71	1.43

Foreign studies have shown that patients heal equally well with 150 mg b.i.d. and 300 mg h.s. (85% versus 84%, respectively) during a usual 4-week course of therapy. If patients require extended therapy of 8 weeks, the healing rate may be higher for 150 mg b.i.d. as compared to 300 mg h.s. (92% versus 87%, respectively).

Studies have been limited to short-term treatment of acute duodenal ulcer. Patients whose ulcers healed during therapy had recurrences of ulcers at the usual rates.

Maintenance Therapy in Duodenal Ulcer: Ranitidine has been found to be effective as maintenance therapy for patients following healing of acute duodenal ulcers. In two independent, double-blind, multicenter, controlled trials, the number of duodenal ulcers observed was significantly less in patients treated with ranitidine (150 mg h.s.) than in patients treated with placebo over a 12-month period.

Duodenal Ulcer Prevalence

Double-blind, Multicenter, Placebo-controlled Trials					
Multicenter Trial	Drug	Duodenal Ulcer Prevalence			No. of Patients
		0-4 Months	0-8 Months	0-12 Months	
USA	RAN	20%*	24%*	35%*	138
	PLC	44%	54%	59%	139
Foreign	RAN	12%*	21%*	28%*	174
	PLC	56%	64%	68%	165

% = Life-table estimate.
* = $p < 0.05$ (Ranitidine versus comparator).
RAN = ranitidine.
PLC = placebo.

As with other H_2-antagonists, the factors responsible for the significant reduction in the prevalence of duodenal ulcers include prevention of recurrence of ulcers, more rapid healing of ulcers that may occur during maintenance therapy, or both.

Gastric Ulcer: In a multicenter, double-blind, controlled, US study of endoscopically diagnosed gastric ulcers, earlier healing was seen in the patients treated with ranitidine as shown in the following table:

	Ranitidine*		Placebo*	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	92	16/83 (19%)	94	10/83 (12%)
Week 6		50/73 (68%)†		35/69 (51%)

* All patients were permitted p.r.n. antacids for relief of pain.
† $p = 0.009$.

In this multicenter trial, significantly more patients treated with ranitidine became pain-free during therapy.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): Ranitidine inhibits gastric acid secretion and reduces occurrence of diarrhea, anorexia, and pain in patients with pathological hypersecretion associated with Zollinger-Ellison syndrome, systemic mastocytosis, and other pathological hypersecretory conditions (e.g., postoperative, "short-gut" syndrome, idiopathic). Use of ranitidine was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

Gastroesophageal Reflux Disease (GERD): In two multicenter, double-blind, placebo-controlled, 6-week trials performed in the United States and Europe, ranitidine 150 mg b.i.d. was more effective than placebo for the relief of heartburn and other symptoms associated with GERD. Ranitidine-treated patients consumed significantly less antacid than did placebo-treated patients.

The US trial indicated that ranitidine 150 mg b.i.d. significantly reduced the frequency of heartburn attacks and severity of heartburn pain within 1 to 2 weeks after starting therapy. The improvement was maintained throughout the 6-week trial period. Moreover, patient response rates demonstrated that the effect of heartburn extends through both the day and night time periods.

In two additional U.S. multicenter, double-blind, placebo-controlled, 2-week trials, ranitidine 150 mg b.i.d. was shown to provide relief of heartburn pain within 24 hours of initiating therapy and a reduction in the frequency and severity of heartburn.

(See Reverse)

Erosive Esophagitis: In two multicenter, double-blind, randomized, placebo-controlled, 12-week trials performed in the United States, ranitidine 150 mg q.i.d. was significantly more effective than placebo in healing endoscopically-diagnosed erosive esophagitis and in relieving associated heartburn. The erosive esophagitis healing rates were as follows:

EROSIVE ESOPHAGITIS PATIENT HEALING RATES

	Healed/Evaluable			
	Placebo* n = 229		Ranitidine 150 mg q.i.d.* n = 215	
Week 4	43/198	(22%)	96/206	(47%)
Week 8	63/176	(36%)	142/200	(71%)
Week 12	92/159	(58%)	162/192	(84%)

* All patients were permitted p.r.n. antacids for relief of pain.
+ $p<0.001$ versus placebo.

No additional benefit in healing of esophagitis or in relief of heartburn was seen with a ranitidine dose of 300 mg q.i.d.

INDICATIONS AND USAGE: Ranitidine tablets are indicated in:
1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than eight weeks.
2. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers. No placebo-controlled comparative studies have been carried out for periods of longer than 1 year.
3. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of active, benign gastric ulcer. Most patients heal within 6 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated, benign gastric ulcer for periods of more than 6 weeks.
5. Treatment of GERD. Symptomatic relief commonly occurs within 24 hours after starting therapy with ranitidine 150 mg b.i.d.
6. Treatment of endoscopically-diagnosed erosive esophagitis. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with ranitidine 150 mg q.i.d.

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; GERD; and erosive esophagitis.

CONTRAINDICATIONS: Ranitidine tablets are contraindicated in patients known to have hypersensitivity to the drug or any of the ingredients (see PRECAUTIONS).

PRECAUTIONS:

General:
1. Symptomatic response to ranitidine therapy does not preclude the presence of gastric malignancy.
2. Since ranitidine is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ranitidine is metabolized in the liver.
3. Rare reports suggest that ranitidine may precipitate acute porphyric attacks in patients with acute porphyria. Ranitidine should therefore be avoided in patients with a history of acute porphyria.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ranitidine therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ranitidine has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ranitidine may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent effect on absorption or a change in volume of distribution).

Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg per day, no interaction occurred; ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has not been investigated.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in life span studies in mice and rats at dosages up to 2,000 mg/kg per day.

Ranitidine was not mutagenic in standard bacterial tests *(Salmonella, Escherichia coli)* for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ranitidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Ranitidine is secreted in human milk. Caution should be exercised when ranitidine is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age-groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age-groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ranitidine. The relationship to ranitidine therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ranitidine administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported. Rare reports of reversible involuntary motor disturbances have been received.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias and myalgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ranitidine and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ranitidine has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ranitidine, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases of erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: There has been limited experience with overdosage. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience (see ADVERSE REACTIONS). In addition, abnormalities of gait and hypotension have been reported.

When overdosage occurs, the usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive

twice the pretreatment levels in 6 of 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias and myalgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ranitidine and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ranitidine has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ranitidine, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases of erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: There has been limited experience with overdosage. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience (see ADVERSE REACTIONS). In addition, abnormalities of gait and hypotension have been reported.

When overdosage occurs, the usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy should be employed.

Studies in dogs receiving dosages of ranitidine in excess of 225 mg/kg per day have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1,000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in mice and rats were 77 and 83 mg/kg, respectively.

DOSAGE AND ADMINISTRATION:

Active Duodenal Ulcer: The current recommended adult oral dosage of ranitidine for duodenal ulcer is 150 mg twice daily. An alternative dosage of 300 mg once daily after the evening meal or at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated (see CLINICAL PHARMACOLOGY, Clinical Trials: *Active Duodenal Ulcer*). Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in US studies, and several foreign trials have shown that 100 mg b.i.d. is as effective as the 150 mg dose.

Antacid should be given as needed for relief of pain (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Maintenance of Healing of Duodenal Ulcers: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ranitidine 150 mg doses more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g per day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Erosive Esophagitis: The current recommended adult oral dosage is 150 mg four times a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ranitidine, the recommended dosage in patients with a creatinine clearance less than 50 mL/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Ranitidine tablets USP, for oral administration, are supplied as:

150 mg: round, off-white, unscored tablets, film-coated pink, debossed GG 705 on one side and plain on the reverse side, in bottles of 60, 100, 500 and 1000.

300 mg: round, off-white, unscored tablets, film-coated orange, debossed GG 706 on one side and plain on the reverse side, in bottles of 30, 250 and 1000.

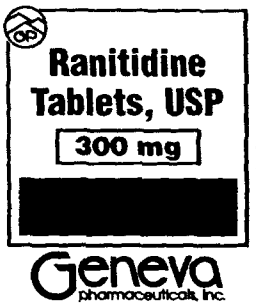
Store at controlled room temperature 15°-30°C (59°-86°F). Store in a dry place, and protect from light. Replace cap securely after each opening.

Dispense in a tight, light-resistant container.

Caution: Federal law prohibits dispensing without prescription.

Rev. 97-4M C97/5
7162-6

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020



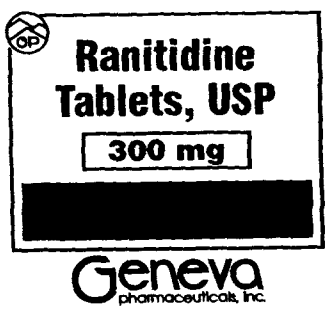
N 3 0781-1884-31 8

Each tablet contains: Ranitidine hydrochloride equivalent to 300 mg of ranitidine.
Usual Dosage: See package insert.
Store at controlled room temperature 15º-30ºC (59º-86ºF) in a dry place. Protect from light. Replace cap securely after each opening. Dispense in a tight, light-resistant container. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
Rev. 96-6M N96/6

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP.:



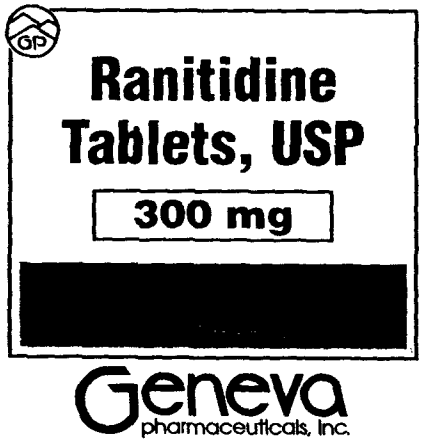
N 3 0781-1884-25 7

Each tablet contains: Ranitidine hydrochloride equivalent to 300 mg of ranitidine.
Usual Dosage: See package insert.
Store at controlled room temperature 15º-30ºC (59º-86ºF) in a dry place. Protect from light. Replace cap securely after each opening. Dispense in a tight, light-resistant container. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
Rev. 96-6M N96/6

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP.:



N 3 0781-1884-10 3

Each tablet contains: Ranitidine hydrochloride equivalent to 300 mg of ranitidine.
Usual Dosage: See package insert.
Store at controlled room temperature 15º-30ºC (59º-86ºF) in a dry place. Protect from light. Replace cap securely after each opening. Dispense in a tight, light-resistant container.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Rev. 96-6M C96/6

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP.:

Ranitidine Tablets, USP

150 mg

[redacted]

Geneva pharmaceuticals, Inc.

N 3 0781-1883-60 1

Each tablet contains: Ranitidine hydrochloride equivalent to 150 mg of ranitidine.
Usual Dosage: See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F) in a dry place. Protect from light. Replace cap securely after each opening. Dispense in a tight, light-resistant container. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
Rev. 96-6M N96/6

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP.:

AUG 29 1997

Ranitidine Tablets, USP

150 mg

[redacted]

Geneva pharmaceuticals, Inc.

N 3 0781-1883-01 4

Each tablet contains: Ranitidine hydrochloride equivalent to 150 mg of ranitidine.
Usual Dosage: See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F) in a dry place. Protect from light. Replace cap securely after each opening. Dispense in a tight, light-resistant container. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
Rev. 96-6M N96/6

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP.:

AUG 29 1997

Ranitidine Tablets, USP

150 mg

[redacted]

Geneva pharmaceuticals, Inc.

N 3 0781-1883-05 2

Each tablet contains: Ranitidine hydrochloride equivalent to 150 mg of ranitidine.
Usual Dosage: See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F) in a dry place. Protect from light. Replace cap securely after each opening. Dispense in a tight, light-resistant container. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
Rev. 96-6M N96/6

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP.:

AUG 29 1997

Ranitidine Tablets, USP

150 mg

[redacted]

Geneva pharmaceuticals, Inc.

N 3 0781-1883-10 6

Each tablet contains: Ranitidine hydrochloride equivalent to 150 mg of ranitidine.
Usual Dosage: See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F) in a dry place. Protect from light. Replace cap securely after each opening. Dispense in a tight, light-resistant container.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Rev. 96-6M C96/6

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP.:

AUG 29 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74467

CHEMISTRY REVIEW(S)

Patients at Reduced Dosage After Healing Acute Ulcers, will not be contained in the insert labeling of this ANDA because they expire post July 25, 1997.

BIO ISSUES: ~~**Pending.**~~ Bio found acceptable on Dec. 18, 1995.

ALL INACTIVE INGREDIENTS CITED? **Yes**
OTHER KEY ISSUES:

APPROVAL SUMMARY

CONTAINER LABELS: **1000s (150 mg and 300 mg) - June 8, 1995**

CARTON LABELING (SUBMISSION DATE): None

INSERT LABELING: **November 22, 1995 (Rev. 95-11M)**

FORMULATION/SCORING SUMMARY: **Same as the NDA. Both the 150 mg and 300 mg tablets are NOT scored. The firm revised the shape of the 300 mg tablet to be round.**

COMMENTS OR FUTURE REVISIONS NEEDED: **CONTRAINDICATIONS - Insert (see PRECAUTIONS) at the end of the sentence.**

1° REVIEWER: /S/ 11/29/95

2° REVIEWER:

SUPERVISOR: /S/

DATE: 11/29/95

Division Review Summary

ANDA: 74-467 **DRUG PRODUCT:** Ranitidine Hydrochloride I

FIRM: Geneva Pharmaceutical

DOSAGE FORM: Coated Tablets

STRENGTHS: 150 mg & 300 mg

CGMP STATEMENT/EIR UPDATE STATUS:
Pending results (update submitted 11/16/95).

BIO INFORMATION:
The Division of bioequivalence found the in-vivo studies for Ranitidine Tablet 300 mg strength (lot No. 6493066) in comparison to the innovator's drug product Zantac tablet 300 mg to be incomplete. A Bio deficiency letter was issued on 1/9/95. Pending review of Bio amendment dated 2/24/95.

VALIDATION:
N/A

STABILITY:
Accelerated stability data (40°C and 75% RH) on the smallest (60's) and largest (1,000's) of the container sizes. These data were found to conform to specified limits.

The stability protocol is in conformance with FDA Guidelines. Containers used in the stability studies are the same as those in the container/closure section of the application. The firm wishes to market the finished drug product only in 1,000's. This is reflected in their revised labeling.

LABELING:
Satisfactory, dated 11/28/95.

SIZE OF BIO BATCH:
A batch record for lot No. 6493066, for the 300 mg tablets is appended. A total of tablets were manufactured.

A batch record for lot No. 6493065, for the 150 mg tablets is appended. A total of tablets were manufactured.

DMF # , drug substance manufacturer for Ranitidine Hydrochloride (Form I), was reviewed by E. Ramos and found to be satisfactory, dated July 29, 1995.

SIZE OF STABILITY BATCHES:
Same as the Bio batch.

PROPOSED PRODUCTION BATCH:
a) 150 mg; units.
b) 300 mg; units.

RECOMMENDATION:
Recommend approval of generic drug Ranitidine Hydrochloride Tablets, 150 mg & 300 mg.

CHEMISTRY REVIEWER: **DATE:** December 5, 1995
Edwin Ramos

/S/ 1/2/96

SUPERVISOR:
Ms. Brenda Arnwine

/S/ 1/8/96

ANDA Approval Summary

74-467
ANDA Number

Geneva Pharmaceutical
Applicant Name

Ranitidine Hydrochloride
Established Name of Drug

Tablets
Dosage Form

150 mg & 300 mg
Strength

150 mg--625 cc (1,000's) & 300 mg--1300 cc (1,000's)
Container Size(s)

	Date found Satisfactory	Comment
Labeling	11/28/95	
Chemistry	12/5/95	
GMP's	12/28/95	
Manufacturer-Finished Dosage Form	12/28/95	
Outside Facilities	12/28/95	
Manufacturer(s)-Active Ingredient(s)	12/28/95	

/S/ 1/18/96
Chemist Reviewer — Date

/S/ 1/18/96
Branch Chief — Date

Petition Required ✓ NO ____ YES

Listed Drug Information 505 (j)(2)(A) 3/8/94

Patent Certification 505 (j)(2)(B) 3/8/94

Date Patent/Exclusivity Expires (if applicable)

Patents: 4658 7/25/97; 4731 6/4/02; 4636 5/13/05 (N/A)

Exclusivity: I-120 3/24/98; I-75 5/19/95; D-21 2/25/97; I-116 11/3/97

Bioequivalence Section

Dissolution Required? ____ No ✓ Yes : ____ DB ____ DGD

In vivo study(s) required? ____ No ✓ Yes

300 mg tablet

Study(s) Found Acceptable	12/18/95	300 mg
Waiver Request Granted	12/18/95	150 mg
Total Bioequivalence Requirement Met	12/18/95	

/S/
Administrative Reviewer

1/25/96
Date

Approved _____

Disapproved _____

_____ _____
Director, Division of Chemistry Date

Comments:

1. CHEMIST'S REVIEW NO. 2

2. ANDA # 74-467

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, Colorado 80038-0446

4. LEGAL BASIS for ANDA SUBMISSION
Ranitidine Hydrochloride Tablets, USP, 150 mg and 300 mg are the generic version of the listed drug, **Zantac** 150 mg and 300 mg manufactured by Glaxo. Patent # 4,128,658 which covers Polymorphic Form I will expire on December 5, 1995. Patent #4,521,431 which covers Polymorphic Form II will expire on the year of 2002.

5. SUPPLEMENT
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Ranitidine Hydrochloride

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

9. AMENDMENTS AND OTHER DATES:
Firm:
February 16, 1994-- Original Submission
March 2, 1994-- Telecom Amendment
March 11, 1994-- ANDA New Correspondence
March 21, 1994-- ANDA New Correspondence
November 11, 1994-- ANDA Original Amendment
February 24, 1995-- Bio-New Correspondence

FDA:
February 23, 1994-- Memo by G. Johnston
March 2, 1994-- Telecom Memo by C. Parise
March 8, 1994-- FTR Memo by G. Johnston
March 8, 1994-- Acknowledgement Receipt
March 21, 1994-- Telecom Memo by C. Parise
June 22, 1994-- Deficiency letter
January 9, 1995-- Bio deficiency letter

10. PHARMACOLOGICAL CATEGORY
H2 Receptor Antagonist

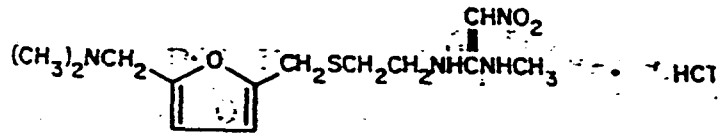
11. Rx or OTC
Rx

12. RELATED DMFs #

13. DOSAGE FORM
Coated Tablets

14. POTENCY
150 mg/300 mg

15. CHEMICAL NAME AND STRUCTURE
N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride.



16. RECORDS AND REPORTS
N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend not approval letter to issue (MAJOR).

19. REVIEWER:
Edwin Ramos

DATE COMPLETED:
February 3, 1995

/S/

3/13/95

(cc Appendix)
3/13/95

Redacted 11

pages of trade

secret and/or

confidential

commercial

information

Chem #2

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 74-467

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, Colorado 80038-0446

4. LEGAL BASIS for ANDA SUBMISSION
Ranitidine Hydrochloride Tablets, USP, 150 mg and 300 mg are the generic version of the listed drug, **Zantac** 150 mg and 300 mg manufactured by Glaxo. Patent # 4,128,658 which covers Polymorphic Form I will expire on December 5, 1995. Patent #4,521,431 which covers Polymorphic Form II will expire on the year of 2002.

5. SUPPLEMENT
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Ranitidine Hydrochloride

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

9. AMENDMENTS AND OTHER DATES:

Firm:

February 16, 1994--	Original Submission
March 2, 1994--	Telecom Amendment
March 11, 1994--	ANDA New Correspondence
March 21, 1994--	ANDA New Correspondence
November 11, 1994--	ANDA Original Amendment
February 24, 1995-	Bio-New Correspondence
June 8, 1995--	ANDA Original Amendment

FDA:

February 23, 1994--	Memo by G. Johnston
March 2, 1994--	Telecom Memo by C. Parise
March 8, 1994--	FTR Memo by G. Johnston
March 8, 1994--	Acknowledgement Receipt
March 21, 1994--	Telecom Memo by C. Parise
June 22, 1994--	Deficiency letter
January 9, 1995--	Bio deficiency letter
March 17, 1995--	Deficiency letter

10. PHARMACOLOGICAL CATEGORY
H2 Receptor Antagonist

11. Rx or OTC
Rx

12. RELATED DMFs #

13. DOSAGE FORM
Coated Tablets

14. POTENCY
150 mg/300 mg

15. CHEMICAL NAME AND STRUCTURE
N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride.

16. RECORDS AND REPORTS
N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend not approval letter to issue. Professional Labeling Review was found deficient dated 8/28/95. No chemistry issues are pending.

19. REVIEWER:
Edwin Ramos

DATE COMPLETED:
July 29, 1995

/S/ 10/23/95

/S/ 10/24/95

Redacted 10

pages of trade

secret and/or

confidential

commercial

information

Chem #3

1. CHEMIST'S REVIEW NO. 4

2. ANDA # 74-467

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, Colorado 80038-0446

4. LEGAL BASIS for ANDA SUBMISSION
Ranitidine Hydrochloride Tablets, USP, 150 mg and 300 mg are the generic version of the listed drug, **Zantac** 150 mg and 300 mg manufactured by Glaxo. Patent # 4,128,658 which covers Polymorphic Form I will expire on December 5, 1995. Patent #4,521,431 which covers Polymorphic Form II will expire on the year of 2002.

5. SUPPLEMENT
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Ranitidine Hydrochloride

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

9. AMENDMENTS AND OTHER DATES:

Firm:

February 16, 1994--	Original Submission
March 2, 1994--	Telecom Amendment
March 11, 1994--	ANDA New Correspondence
March 21, 1994--	ANDA New Correspondence
November 11, 1994--	ANDA Original Amendment
February 24, 1995-	Bio-New Correspondence
June 8, 1995--	ANDA Original Amendment
October 27, 1995--	New Correspondence-Bio
November 22, 1995--	ANDA Original Amendment
January 22, 1996--	Minor Telecom Amendment

FDA:

February 23, 1994--	Memo by G. Johnston
March 2, 1994--	Telecom Memo by C. Parise
March 8, 1994--	FTR Memo by G. Johnston
March 8, 1994--	Acknowledgement Receipt
March 21, 1994--	Telecom Memo by C. Parise
June 22, 1994--	Deficiency letter
January 9, 1995--	Bio deficiency letter
March 17, 1995--	Deficiency letter
August 28, 1995--	Labeling review
October 27, 1995--	Deficiency letter
January 22, 1996--	Telecom

10. PHARMACOLOGICAL CATEGORY
H2 Receptor Antagonist

11. Rx or OTC
Rx

12. RELATED DMFs #

13. DOSAGE FORM
Coated Tablets

14. POTENCY
150 mg/300 mg

15. CHEMICAL NAME AND STRUCTURE
N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Updated room temperature stability data (24 months) for the 150 mg and 300 mg obtained in the smallest and largest of the marketing containers were provided per our request. All critical assays were found to conform to specifications. However, the organoleptic analysis for the 150 mg tablets shows a slight darkening of the coated tablet at the 24 months test station. The request for a 36 months expiry should consider the organoleptic results.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval letter to issue.

19. REVIEWER:
Edwin Ramos

DATE COMPLETED:
December 5, 1995

/S/ 1/22/96

/S/ 1/22/96

Redacted 11

pages of trade

secret and/or

confidential

commercial

information

Chem #4

H2 1

1. CHEMIST'S REVIEW NO. 5

2. ANDA # 74-467

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, Colorado 80038-0446

4. LEGAL BASIS for ANDA SUBMISSION
Ranitidine Hydrochloride Tablets, USP, 150 mg and 300 mg are the generic version of the listed drug, **Zantac** 150 mg and 300 mg manufactured by Glaxo. Patent # 4,128,658 which covers Polymorphic Form I will expire on July, 1997.

5. SUPPLEMENT
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Ranitidine Hydrochloride

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

9. AMENDMENTS AND OTHER DATES:

Firm:

February 16, 1994--	Original Submission
March 2, 1994--	Telecom Amendment
March 11, 1994--	ANDA New Correspondence
March 21, 1994--	ANDA New Correspondence
November 11, 1994--	ANDA Original Amendment
February 24, 1995-	Bio-New Correspondence
June 8, 1995--	ANDA Original Amendment
October 27, 1995--	New Correspondence-Bio
November 22, 1995--	ANDA Original Amendment
January 22, 1996--	Minor Telecom Amendment
January 30, 1996--	Telephone Amendment
March 13, 1997--	Amendment

FDA:

February 23, 1994--	Memo by G. Johnston
March 2, 1994--	Telecom Memo by C. Parise
March 8, 1994--	FTR Memo by G. Johnston
March 8, 1994--	Acknowledgment Receipt
March 21, 1994--	Telecom Memo by C. Parise
June 22, 1994--	Deficiency letter
January 9, 1995--	Bio deficiency letter
March 17, 1995--	Deficiency letter
August 28, 1995--	Labeling review
October 27, 1995--	Deficiency letter
January 22, 1996--	Telecom
January 31, 1996--	TA letter

Edw

10. PHARMACOLOGICAL CATEGORY
H2 Receptor Antagonist

11. Rx or OTC
Rx

12. RELATED DMFs #

13. DOSAGE FORM
Coated Tablets

14. POTENCY
150 mg & 300 mg

15. CHEMICAL NAME AND STRUCTURE
N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
18 and 13 months of room temperature data for the 150 mg and 300 mg, respectively, were submitted to validate the additional container/closure systems. Also, accelerated stability data are included. These data are found to conform to the tentatively approved specifications (attachment 2 & 3, 3/13/97). Packaging specifications are provided. The proposed container/closure systems do not affect the manufacturing equipment, processes and formula. All pertinent information for the additional container closure systems are included (attachment 4).

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval letter to issue. Chemistry review only, no letter will be issued. Awaiting decision from General Counsel.

19. REVIEWER:
Edwin Ramos
/S/

DATE COMPLETED:
April 16, 1997
4/30/97

Redacted 10

pages of trade

secret and/or

confidential

commercial

information

Chem # 5

1. CHEMIST'S REVIEW NO. 6

2. ANDA # 74-467

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, Colorado 80038-0446

4. LEGAL BASIS for ANDA SUBMISSION
Patent # 4,128,658 which covers Polymorphic Form I will expire July 25, 1997.

5. SUPPLEMENT
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Ranitidine Hydrochloride

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

9. AMENDMENTS AND OTHER DATES:

Firm:

February 16, 1994--	Original Submission
March 2, 1994--	Telecom Amendment
March 11, 1994--	ANDA New Correspondence
March 21, 1994--	ANDA New Correspondence
November 11, 1994--	ANDA Original Amendment
February 24, 1995-	Bio-New Correspondence
June 8, 1995--	ANDA Original Amendment
October 27, 1995--	New Correspondence-Bio
November 22, 1995--	ANDA Original Amendment
January 22, 1996--	Minor Telecom Amendment
January 30, 1996--	Telephone Amendment
March 13, 1997--	Amendment
April 24, 1997--	Amendment

FDA:

February 23, 1994--	Memo by G. Johnston
March 2, 1994--	Telecom Memo by C. Parise
March 8, 1994--	FTR Memo by G. Johnston
March 8, 1994--	Acknowledgment Receipt
March 21, 1994--	Telecom Memo by C. Parise
June 22, 1994--	Deficiency letter
January 9, 1995--	Bio deficiency letter
March 17, 1995--	Deficiency letter
August 28, 1995--	Labeling review
October 27, 1995--	Deficiency letter
January 22, 1996--	Telecom
January 31, 1996--	TA letter
April 16, 1997--	Chemistry review--acceptable

April 24, 1997-- Labeling review-acceptable
June 1, 1997-- Info letter
July 15, 1997-- Info letter

10. PHARMACOLOGICAL CATEGORY
H2 Receptor Antagonist

11. Rx or OTC
Rx

12. RELATED DMFs #

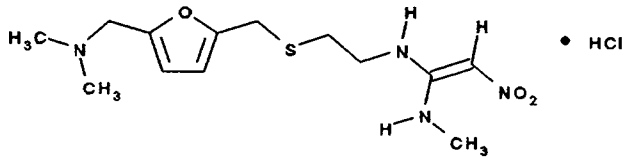
13. DOSAGE FORM
Coated Tablets

14. POTENCY
150 mg & 300 mg

15. CHEMICAL NAME AND STRUCTURE

Ranitidine Hydrochloride USP

$C_{13}H_{22}N_4O_3S.HCl$; M.W. = 350.87



N-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride.
CAS [66357-59-3]

16. RECORDS AND REPORTS
N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval letter to issue.

19. REVIEWER:
Edwin Ramos
/S/

DATE COMPLETED:
August 28, 1997
8/28/97

Redacted 11

pages of trade

secret and/or

confidential

commercial

information

Chem # 6

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74467

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA: #74-467 **SPONSOR:** Geneva Pharmaceuticals
Drug: Ranitidine HCl
DOSAGE FORM: Tablets
STRENGTH: 300 mg
TYPE OF STUDY: Single/Fasting
CLINICAL SITE:
ANALYTICAL SITE:

STUDY SUMMARY:

Twenty-six (26) healthy male volunteers participated and completed the study. Blood samples were collected from 0.0 - 24.0 hours. Serum levels of ranitidine were measured using assay method. The 90% confidence intervals calculated for the Ln-transformed parameters of AUC (0-T), AUC(0-Inf), and C(max) fall in the acceptable range of 80% - 125%. The bioequivalence study conducted under fasting conditions has been found acceptable by the Division of Bioequivalence.

DISSOLUTION:

The dissolution testing conducted on 12 units of the test and reference products are acceptable. Not Less Than 80% (Q) of the labeled amount was dissolved in 45 minutes

PRIMARY REVIEWER: F. Nouravarsani **BRANCH:** III

SIGNITURE: /S/ **DATE:** 12/19/95

BRANCH CHIEF: R. Mhatre **BRANCH:** III

SIGNITURE: /S/ **DATE:** 12/19/95

DIRECTOR: K. Chan
DIVISION OF BIOEQUIVALENCE:

SIGNITURE: /S/ **DATE:** 1/31/96

DIRECTOR:
OFFICE OF GENERIC DRUGS:

SIGNITURE: _____ **DATE:** _____

DEC 18 1995

Ranitidine HCl Tablets
USP, 300 & 150 mg
ANDA #74-467
Reviewer: F. Nouravarsani
74467ADW.295

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
February 24, 1995
October 27, 1995

REVIEW OF BIOEQUIVALENCE STUDY AMENDMENTS, DISSOLUTION TESTING AND A WAIVER REQUEST

INTRODUCTION:

Geneva Pharmaceuticals, Inc. has responded to the Division of Bioequivalence deficiency letter dated January 09, 1995.

The firm had submitted a fasting bioequivalence study and dissolution testing conducted on its test product, Ranitidine Hydrochloride Tablets, 300 mg, and Zantac Tablets, Ranitidine Hydrochloride, 300 mg, manufactured by Glaxo Pharmaceuticals (NDA #18703-002) as the listed reference product.

Deficiency #1:

The samples from all 26 subjects were assayed by error, but the data from 24 subjects were analyzed statistically. The firm was requested to submit the data for all of the subjects, and conduct statistical data analyses using all 26 subjects.

Response to Deficiency #1:

The data were reanalyzed statistically to include subjects #25 and #26. The pharmacokinetic parameters are compared in Table 1.

The AUC(0-T) for the test product, 5176.6 hr*ng/mL, is comparable with the AUC(0-T) of 5166.8 hr*ng/mL for the reference product.

The AUC(0-Inf) for the test product, 5218.0 hr*ng/mL, is comparable with the one obtained for the reference product, 5203.8 hr*ng/mL.

The C(Max) for the test product, 1124.4 ng/mL, is comparable with the C(Max) of 1109.2 ng/mL for the reference product.

Results of the GLM statistical data analyses were not included in the submission dated February 24, 1995. This information was submitted on October 27, 1995 in response to phone call by Dr. Jason Gross. There are no product, period (p=0.05) and sequence (p=0.1) effects observed for the pharmacokinetic parametetrs using Ln-transformed or un-transformed parameters.

The 90% confidence intervals for ln-transformed parameters, AUC(0-T), AUC(0-Inf), and C(Max) fall in the required range by the Division of Bioequivalence (summarized in Table 1).

No errors were found by spot checking of the calculations and statistical data analysis.

Samples from subjects #25 and #26 were assayed with runs BWE 18 and BWE 19, respectively. The accuracy and precision for the Standard and Quality Control Samples including all runs are summarized as follows:

Accuracy:

(a) From the standard samples, interday-
concentration range of ng/mL: %

(b) From the quality control samples, interday-
concentration of ng/mL: 95.5% (N=35)
concentration of ng/mL: 103.6% (N=42)
concentration of ng/mL: 98.8% (N=41)

Precision:

(a) From the standard samples, interday-
concentration range of ng/mL: %

(b) From the quality control samples, interday-
concentration of ng/mL: 10.1% (N=35)
concentration of ng/mL: 11.0% (N=42)
concentration of ng/mL: 10.1% (N=41)

Reviewer Comment:

The firm's response is acceptable.

Deficiency #2:

Limit Of Quantification (LOQ) was set at ng/mL. The firm was advised to increase the LOQ to a higher value, since significant interferences were observed for the following subject samples:

Response to Deficiency #2:

has stated that a higher LOQ will be set for ranitidine studies in the future. However, Cmax values were higher than 400 times the LOQ. Therefore, the bioequivalence study should not be affected by this interference.

Reviewer Comment:

The response is acceptable for this study.

Deficiency #3:

The firm was requested to report all original values together with reassayed, values which were used in the study, reason for reassaying, and rationale for the used values summarized in a table.

Response to Deficiency #3:

The firm had not submitted the original or reassayed values for all of the reanalyzed samples in its amendment dated February 24, 1995. These information were requested by phone call of Dr. Jason Gross. The values for all of the reassayed samples were submitted in the current amendment (submition date: October 27, 1995).

Reviewer Comment:

The response is acceptable.

Deficiency #4:

The waiver request for bioequivalence study requirements for 150 mg Ranitidine HCl Tablets was not granted, since the bio-study conducted on 300 mg Tablets was found incomplete.

Response to Deficiency #4:

The firm has resubmitted its request for waiver of bioequivalence study requirements for Ranitidine Tablets, 150 mg based on:

a. the bioequivalence study conducted on the 300 mg strength,

b. the comparative dissolution testing conducted on 300 mg and 150 mg of the test and reference products (Table 2), and

c. the similar composition of the products (Table 3).

The results of the in vitro studies are summarized as follows:

Dissolution Testing:

A. Results of the dissolution testing conducted on 12 units of the test product, Ranitidine Tablets, 300 mg (lot #6493066) and the reference product, Zantac Tablets, 300 mg (lot #Z10203 BP) are shown in Table 2. Not less than % (mean of 12 units) of the labeled amount of ranitidine was dissolved in 45 minutes for the test or reference product using USP XXII method. The dissolution of no unit was less than Q % at 45 minutes.

B. Results of the dissolution testing conducted on 12 units of the test product, 150 mg tablets (lot #6493065) and reference product, 150 mg Zantac tablets (lot #Z10773 FP) are shown in Table 2. Not less than % (mean of 12 units) of the labeled amount of ranitidine was dissolved in 45 minutes for the test or reference product using USP XXII method. The dissolution of no unit was less than Q % at 45 minutes.

Potency:

The assayed potencies of the test products, Ranitidine HCl Tablets, 300 mg, and 150 mg were % (CV = 0.6, N=6) and % (CV = 0.4%, N=6) of the labeled amount claimed, respectively. These values fall in the USP required range of %. The assayed potencies of the reference products was reported as % (CV = 0.8%, N=3)) for the 300 mg tablets, and % (CV =2.1%, N = 6) for 150 mg tablets.

Content Uniformity:

Values of % (CV = 1.4%, N=10) and % (CV = 2.3%, N=10) were obtained as means of percentage of the labeled amount claimed for 10 Ranitidine HCl Tablets, 300 mg, and 150 mg, respectively. The content uniformities of the reference products were % (CV = 1.3%, N=10) for 300 mg Tablets, and % (CV = 1.5%, N=10) for 150 mg Tablets. These values fall in the USP range of % with a CV of NMT %.

Reviewer Comment:

The waiver of bioequivalence study requirements for Ranitidine Tablets, 150 mg may be granted.

Deficiency #5:

It was stated that study samples will be stored frozen until 5/25/94, then they will be discarded. The samples were stored less than one year, since the clinical study was started on October 8, 1993. The firm was informed that the storage period should be increased to at least one year for the future studies.

Response to Deficiency #5:

The firm responded that: "The samples continue to remain in storage at . The statement in the analytical report was incorrect and should indicate that the samples will remain in storage until 25May94 at which time the client will be contacted regarding further retention of stored samples."

Reviewer Comment:

The firm's response is acceptable.

RECOMMENDATIONS:

1. The bioequivalence study conducted by Geneva Pharmaceuticals, Inc. on its Ranitidine HCl Tablets, 300 mg, lot #6493066, comparing it to Zantac Tablets, 300 mg, lot #Z10203BP manufactured by Glaxo Pharmaceuticals has been found acceptable by the Division of Bioequivalence.

2. The dissolution testings conducted by the Geneva Pharmaceuticals, Inc. on its Ranitidine HCl Tablets, 300 mg, lot #6493066, and Ranitidine HCl Tablets, 150 mg, lot #6493065 are acceptable.

3. From the bioequivalence point of view, the firm has met the requirements of in-vivo bioequivalence and in-vitro dissolution testing.

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than ¾ of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

5. Waiver of bioequivalence study requirements may be granted for the firm's Ranitidine HCl Tablets, 150 mg.

/S/

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE /S/
FT INITIALED RMHATRE 12/18/95

Concur: /S/ Date: 12/18/95
for Keith Chan, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/12-08-95/74467ADW.295

Table 1:

Comparison of Mean (CV%) Ranitidine Pharmacokinetic Parameters, and 90% CI (ln-transformed) Obtained for 300 mg Tablets of the Test and Reference Products, N=26:

Parameter	Test	Reference	90% CI (ln-trans.)
AUC(0-T) hr*ng/mL	5176.6(25)	5166.8(22)	92.1% - 107.0%
AUC(0-Inf) hr*ng/mL	5218.0(25)	5203.8(22)	92.3% - 107.1%
C(Max) ng/mL	1124.4(44)	1109.2(38)	87.5% - 110.2%
T(Max) hr	2.602 (33)	2.500 (35)	
K(Elm) 1/hr	0.2205(16)	0.2201(11)	
T(1/2) hr	3.219 (16)	3.192 (12)	

Table 2:

Drug (Generic Name):Ranitidine HCl Tablets, USP
Dose Strength: 300 mg, 150 mg
ANDA: #74-467: Geneva Pharmaceuticals, Inc
Submission Date: February 24, 1995

In Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket ___ Paddle X RPM 50 No. Units Tested 12

Medium: Water at 37° C Volume: 900 mL

Reference Drug, (Manuf.) Zantac, (Glaxo)

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times	Test Product Lot # 6493066			Reference Product Lot # Z10203BP		
Minutes	Strength (mg) 300			Strength (mg) 300		
	Mean%	Range%	(CV%)	Mean %	Range%	(CV%)
15	88.0	-	(08.8)	70.0	-	(11.7)
30	100.0	-	(01.8)	93.0	-	(04.4)
45	100.0	-	(01.9)	97.0	-	(02.5)
60	101.0	-	(01.7)	99.0	-	(01.9)

Sampling Times	Test Product Lot # 6493065			Reference Product Lot # Z10773FP		
Minutes	Strength (mg) 150			Strength (mg) 150		
	Mean%	Range%	(CV%)	Mean %	Range%	(CV%)
15	84.0	-	(13.1)	41.0		(12.4)
30	98.0	-	(01.6)	72.0		(06.0)
45	99.0		(01.6)	89.0		(07.5)
60	99.0		(01.7)	94.0		(04.1)

Table 3:

Formulation Comparison:

Ingredients	150 mg Tablet	300 mg Tablet
Ranitidine HCl, USP	mg(a)	mg(b)
Microcrystalline Cellulose, NF	mg	mg
Hydroxypropyl Methylcellulose 2910 USP	mg	ng
Sodium Starch Glycolate, NF	mg	ng
Magnesium Stearate, NF	mg	mg
Opadry Pink YS-5-1296	mg	
Opadry Orange Y-5-2394		mg
Opadry Clear YS-1-7006	mg	mg
Purified Water		

(a) Equivalent to 150 mg ranitidine base.

(b) Equivalent to 300 mg ranitidine base.

DEC 9 1994

Ranitidine HCl Tablets
300 & 150 mg
ANDA #74-467
Reviewer: F. Nouravarsani
74467SDW.294

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
February 16, 1994

REVIEW OF A BIOEQUIVALENCE STUDY, DISSOLUTION TESTING AND A WAIVER REQUEST

INTRODUCTION:

Geneva Pharmaceuticals, Inc. has submitted a bioequivalence study and dissolution testing conducted on its test product, Ranitidine Hydrochloride Tablets, 300 mg, and Zantac Tablets, Ranitidine Hydrochloride, 300 mg, manufactured by Glaxo Pharmaceuticals (NDA #18703-002) as the listed reference product.

Ranitidine Hydrochloride, a histamine H_2-receptor antagonist inhibits daytime and nocturnal basal gastric acid secretions. It also inhibits the gastric acid secretion stimulated by meal, pentagastrin, and betazole. The oral absolute bioavailability of Zantac is 50%. Mean peak levels of ranitidine are 440 to 545 ng/mL observed at 2 to 3 hours following a 150 mg dose. The administration of food or antacids does not show a significant effect on the absorption of the Zantac. It has been reported in one study that simultaneous administration of Zantac with a high potency antacid (150 m mol) reduced the absorption of Zantac in fasting subjects. The elimination half-life is reported to be 2.5 to 3 hours (PDR 47, 1994).

BIOEQUIVALENCE STUDY:

Objectives:

1. Determine the bioequivalency of the test product, Ranitidine Hydrochloride Tablets, 300 mg and the reference product, Zantac Tablets, 300 mg, under fasting conditions.

2. Compare the in vitro dissolution testing conducted on the test and reference products.

3. Request a waiver of bioequivalence study requirements for Ranitidine Hydrochloride Tablets, 150 mg.

Sponsor: Geneva Pharmaceuticals, Inc., Broomfield, CO
Manufactured by: Geneva Pharmaceuticals, Inc.
Contract Facility:

Study Design:

A single dose of treatment A (test product, lot #6493066, expiration date of September 1995) and treatment B (reference product, lot #Z10203BP, expiration date of February 1995) was administered randomly to healthy volunteers in a two - way crossover study design (protocol/report No. 930825).

Clinical Study Dates:

Phase I: October 8, 1993
Phase II: October 15, 1993
Washout period: 7 days

Subjects:

Twenty six (26) healthy male volunteers were enrolled and completed the study. Subjects number 2, 3, 5, 8, 10, 11, 13, 16, 17, 19, 21, 23, and 25 received treatment A for phase I study. The rest of the volunteers (1, 4, 6, 7, 9, 12, 14, 15, 18, 20, 22, 24, and 26) were dosed treatment A for phase II. The subject age, weight, and height are summarized as following:

Age : 19 - 45 years
Weight: 61.4 - 89.8 kg
Height: 158 - 192 cm

The samples from all 26 subjects were assayed, however statistical data analyses was conducted using subjects 1-24.

Housing, Food and Fluid Intake:

All volunteers were housed in the
from 12 hours prior to the dose administration until after last blood sample collection at 24 hours. The subjects fasted overnight prior to the dosing until 5 hours after the dosing. The standard meals were served 5 hours and 10 hours after the dose. Water was not allowed from 2 hours before the dose until 5 hours after the dose.

Blood Samples:

Blood samples were collected at predose and after the dose at 0.33, 0.50, 0.67, 1.0, 1.33, 1.5, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, and 24.0 hours.

Analytical Procedures:

Limit of Quantitation:

The lower limit of quantitation was set at ng/mL (the lowest non-zero concentration of a standard sample).

Assay Range: ng/mL, using Ln polynomial regression.

Statistical Analysis:

The data were analyzed using SAS - GLM procedure. The two one sided t-test procedure (90% confidence intervals) was used to compare the least square means of the parameters of AUC(0-t), AUC(0-Inf), and C(Max) obtained from the test and reference products.

Medical Events:

The reported non-serious, mild, expected drug related medical events are summarized as follows:

Medical Event	Subject #	Product
Headache	16	Test
Dizziness	4	Ref.
Dizziness on standing up	17	Ref.

Results:

The mean serum concentrations of ranitidine are summarized in Table 1. Linear and semi-ln Plots of the mean plasma concentrations of ranitidine versus time for both test and reference products are shown in Figures I and II. The pharmacokinetic parameters are compared in Table 2.

The AUC(0-T) for the test product, 5284.1 hr*ng/mL, is comparable with the AUC(0-T) of 5182.1 hr*ng/mL for the reference product.

The AUC(0-Inf) for the test product, 5323.7 hr*ng/mL, is comparable with the one obtained for the reference product, 5217.7 hr*ng/mL.

The C(Max) for the test product, 1171.0 ng/mL, is comparable with the C(Max) of 1124.9 ng/mL for the reference product.

Mean AUC(0-T)/AUC(0-Inf) ratios for the test and reference products were 99.2% and 99.3%, respectively (Table 3).

Mean test/reference ratios for AUC(0-T), AUC(0-Inf), and C(Max), were 103.7%, 103.7%, and 107.1%, respectively (Table 4).

The 90% confidence intervals for AUC(0-T), AUC(0-Inf), and C(Max) are summarized as follows:

Parameters	Ln-transformed	Un-transformed
AUC(0-T)	94.0 - 109.4	94.3 - 109.6
AUC(0-Inf)	94.1 - 109.5	94.4 - 109.6
C(Max)	91.1 - 114.4	92.1 - 116.1

There are no product, period (p=0.05) and sequence (p=0.1) effects observed for the above pharmacokinetic parametetrs using Ln-transformed or un-transformed parameters.

IN VITRO STUDIES:

Dissolution Testing:

A. Results of the dissolution testing conducted on 12 units of the test product, Ranitidine Tablets, 300 mg (lot #6493066) and the reference product, Zantac Tablets, 300 mg (lot #Z10203 BP) are shown in Table 5. Not less than % (mean of 12 units) of the labeled amount of ranitidine was dissolved in 45 minutes for the test or reference product using USP XXII method. The dissolution of no unit was less than Q % at 45 minutes.

B. Results of the dissolution testing conducted on 12 units of the test product, 150 mg tablets (lot #6493065) and reference product, 150 mg Zantac tablets (lot #Z10773 FP) are shown in Table 5. Not less than % (mean of 12 units) of the labeled amount of ranitidine was dissolved in 45 minutes for the test or reference product using USP XXII method. The dissolution of no unit was less than Q % at 45 minutes.

Potency:

The assayed potencies of the test products, Ranitidine HCl Tablets, 300 mg, and 150 mg were 98.3% (CV = 0.6, N=6) and % (CV = 0.4%, N=6) of the labeled amount claimed, respectively. These values fall in the USP required range of %. The assayed potencies of the reference products was reported as % (CV = 0.8%, N=3)) for the 300 mg tablets, and % (CV =2.1%, N = 6) for 150 mg tablets.

Content Uniformity:

Values of % (CV = 1.4%, N=10) and 100.8% (CV = 2.3%, N=10) were obtained as means of percentage of the labeled amount

claimed for 10 Ranitidine HCl Tablets, 300 mg, and 150 mg, respectively. The content uniformities of the reference products were % (CV = 1.3%, N=10) for 300 mg Tablets, and % (CV = 1.5%, N=10) for 150 mg Tablets. These values fall in the USP range of with a CV of NMT .

Waiver Request for Ranitidine HCl Tablets, 150 mg:

The firm requested a waiver of bioequivalence study requirements for its Ranitidine HCl Tablets, 150 mg based on "the similar composition of the products, the satisfactory dissolution profiles for the 150 mg strength, and the fact that an in vivo bioavailability study has been conducted on the 300 mg strength".

COMMENTS:

1. Lots #6493066 (test product) and #Z10203BP (reference product) were used for both the bioequivalence study and the dissolution testing. Theoretical batch size was tablets.

2. The dissolution testings conducted on 300 mg and 150 mg Ranitidine HCl Tablets are acceptable.

3. Application Form FDA 356h was not included in the jacket.

DEFICIENCIES:

1. The samples from all 26 subjects were assayed by error, but the data from 24 subjects were analyzed statistically. The firm should submit the data for all of the subjects, and conduct statistical data analyses using all 26 subjects.

2. Limit Of Quantification (LOQ) was set at ng/mL. The firm should be advised to increase the LOQ to a higher value, since significant interference was observed for the following subject samples:

For example the original values for the following samples should be reported:

4. The waiver request for bioequivalence study requirements for 150 mg Ranitidine HCl Tablets may not be granted, since the bio-study conducted on 300 mg Tablets has been found incomplete.

5. It was stated that samples will be stored frozen until 5/25/94, then they will be discarded. The samples were stored less than one year, since the clinical study was started on October 8, 1993. The firm should be informed for the future studies that the storage period should be increased to at least one year.

RECOMMENDATIONS:

1. The bioequivalence study conducted by Geneva Pharmaceuticals, Inc. on its Ranitidine HCl Tablets, 300 mg, lot #6493066, comparing it to Zantac Tablets, 300 mg has been found incomplete by the Division of Bioequivalence.

2. The dissolution testings conducted by the Geneva Pharmaceuticals, Inc. on its Ranitidine HCl Tablets, 300 mg, lot #6493066, and Ranitidine HCl Tablets, 150 mg, lot #6493065 are acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP XXII apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than % of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

The firm should be informed of the DEFICIENCIES and the RECOMMENDATIONS.

/S/

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/

Concur: /S/ Date: 12/9/94
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Table 1:

Mean (CV%) Serum Concentrations (ng/mL) of Ranitidine, N=24:

Time, hr	Test Product		Reference Product	
0.00	0.000	(--)	0.000	(--)
0.33	158.4	(96)	108.8	(69)
0.50	322.9	(63)	292.9	(52)
0.67	414.5	(47)	386.7	(43)
1.00	600.3	(50)	510.2	(41)
1.33	746.0	(71)	607.5	(50)
1.50	721.2	(61)	682.1	(52)
1.67	686.9	(61)	692.5	(54)
2.00	811.0	(56)	747.9	(60)
2.50	880.1	(50)	751.4	(53)
3.00	836.7	(40)	834.4	(36)
3.50	751.0	(38)	772.7	(41)
4.00	668.1	(33)	694.3	(35)
5.00	549.6	(28)	560.2	(32)
6.00	399.1	(30)	410.0	(28)
8.00	250.5	(28)	244.8	(25)
10.00	134.5	(29)	142.0	(26)
12.00	72.1	(30)	73.8	(26)
16.00	29.3	(37)	29.7	(31)
24.00	7.7	(40)	7.5	(40)

Table 2:

Comparison of Mean (CV%) Ranitidine Pharmacokinetic Parameters Obtained for 300 mg Tablets of the Test and Reference Products, N=24:

Parameters	Test Product		Reference Product	
AUC(0-T) hr*ng/mL	5284.1	(24.5)	5182.1	(23.2)
AUC(0-Inf) hr*ng/mL	5323.7	(24.2)	5217.7	(23.0)
C(Max) ng/mL	1171.0	(41.8)	1124.9	(38.3)
T(Max) hr	2.527	(34.1)	2.417	(35.5)
K(Elm) 1/hr	0.223	(14.9)	0.222	(11.1)
T(1/2) hr	3.17	(14.6)	3.16	(12.1)

Table 3: AUC(0-T)/AUC(0-Inf) Percentage

Subject	Test	Reference
01		
02		
03		
04		
05		
06		
07		
08		
09		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
Mean%	99.2	99.3
CV%	0.6	0.4
Range%	%	%

Table 4: Ratio Analysis of the Parameters

	(Test/Reference) Percentage		
Subject	AUC(0-T)	AUC(0-Inf)	C(Max)
01			
02			
03			
04			
05			
06			
07			
08			
09			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
Mean%	103.7	103.7	107.1
CV%	22.0	21.9	32.3
Range%			

Table 5:

Drug (Generic Name):Ranitidine HCl Tablets, USP
Dose Strength: 300 mg, 150 mg
ANDA: #74-467m: Geneva Pharmaceuticals, Inc
Submission Date: February 16, 1994

In Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket ___ Paddle X RPM 50 No. Units Tested 12

Medium: Water at 37° C Volume: 900 mL

Reference Drug, (Manuf.) Zantac, (Glaxo)

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times	Test Product Lot # 6493066			Reference Product Lot # Z10203BP		
Minutes	Strength (mg) 300			Strength (mg) 300		
	Mean%	Range%	(CV%)	Mean %	Range%	(CV%)
15	88.0	-	(08.8)	70.0	-	(11.7)
30	100.0	-	(01.8)	93.0	-	(04.4)
45	100.0	-	(01.9)	97.0	-	(02.5)
60	101.0		(01.7)	99.0	-	(01.9)

Sampling Times	Test Product Lot # 6493065			Reference Product Lot # Z10773FP		
Minutes	Strength (mg) 150			Strength (mg) 150		
	Mean%	Range%	(CV%)	Mean %	Range%	(CV%)
15	84.0	-	13.1)	41.0	-	(12.4)
30	98.0	-	01.6)	72.0	-	(06.0)
45	99.0	-	01.6)	89.0	-	(07.5)
60	99.0	-	(01.7)	94.0	-	(04.1)

Figure I

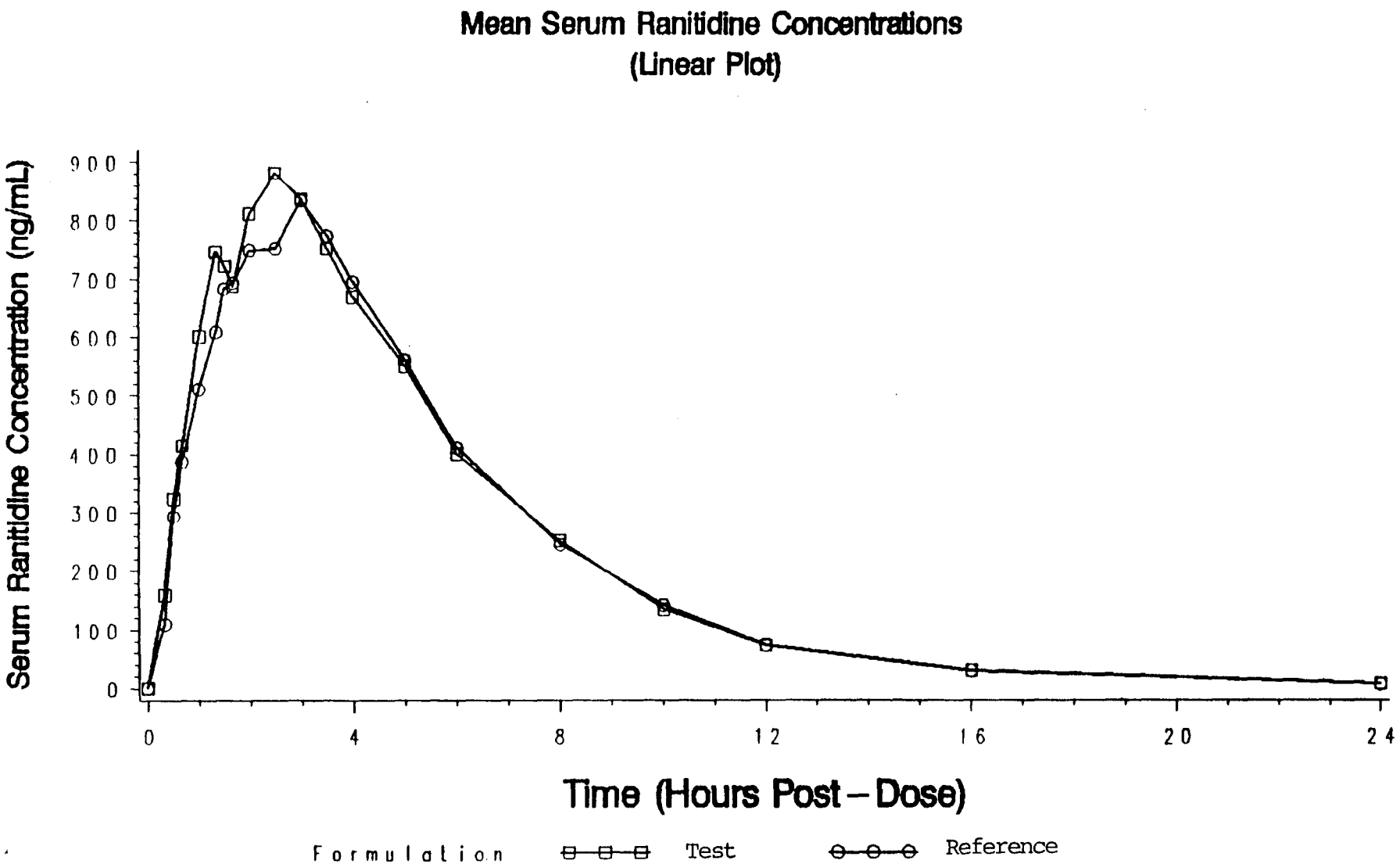
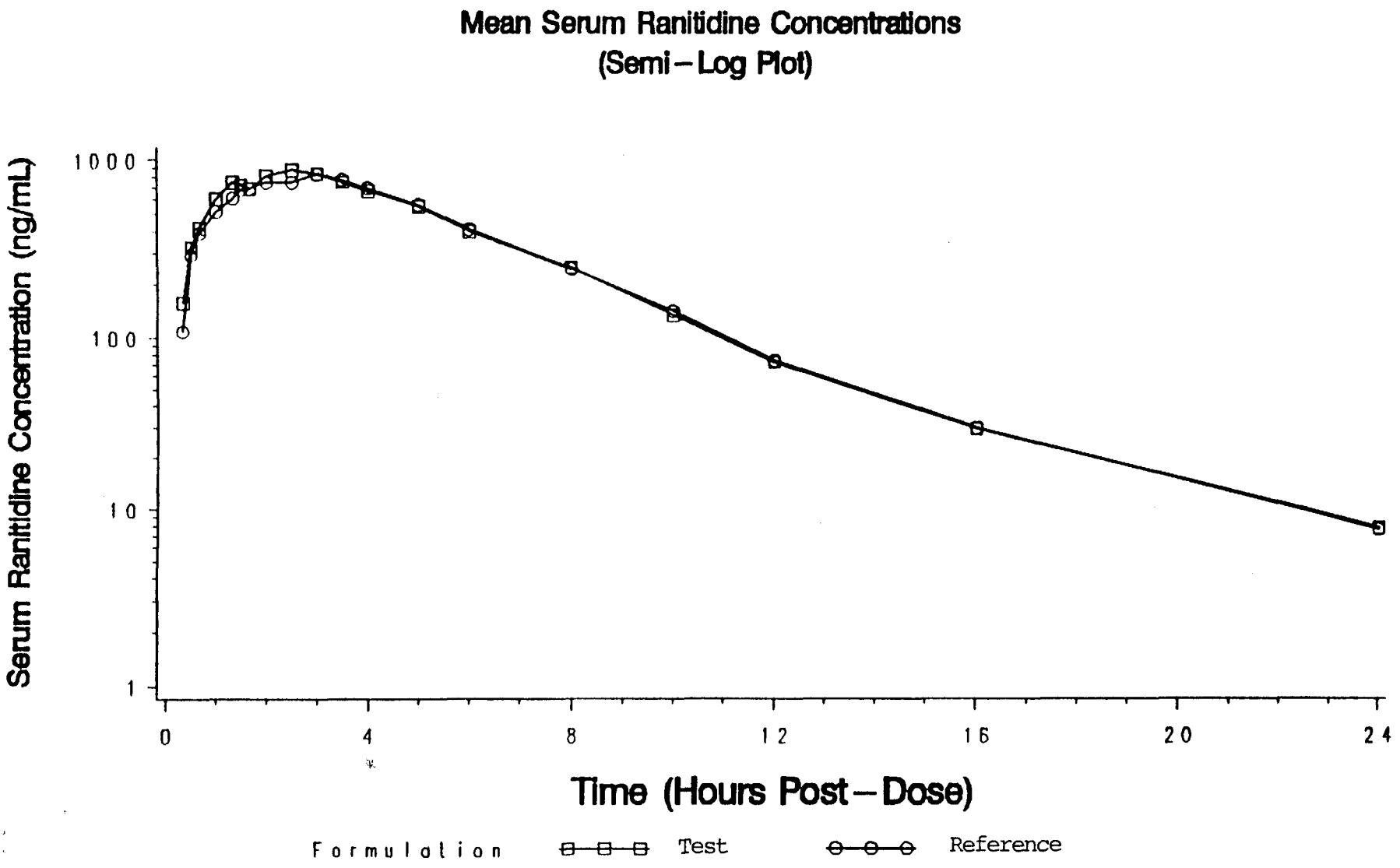

Mean Serum Ranitidine Concentrations
(Linear Plot)
Serum Ranitidine Concentration (ng/mL)
900
800
700
600
500
400
300
200
100
0
0
4
8
12
16
20
24
Time (Hours Post – Dose)
Formulation
Test
Reference

Figure II


Mean Serum Ranitidine Concentrations
(Semi-Log Plot)
Serum Ranitidine Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (Hours Post-Dose)
Formulation
Test
Reference

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74467

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 74-467 Date of Submission: April 24, 1997

Applicant's Name: Geneva Pharmaceuticals, Inc.

Established Name: Ranitidine Tablets USP, 150 mg and 300 mg

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 150 mg (60s, 100s, 500s, 1000s)
300 mg (30s, 250s, 1000s)
Satisfactorily submitted April 24, 1997.

Professional Package Insert Labeling:
Satisfactorily submitted April 24, 1997.

Revisions needed post-approval: The following exclusivities -
I-116 (11/3/97) - Maintenance of Healing of Erosive Esophagitis
I-120 (3/29/98) - Maintenance Therapy for Gastric Ulcer Patients at Reduced Dosage After Healing Acute Ulcers

Container Labels - Asterisk Strength on Main Display Panel and Each tablet" Statement on

BASIS OF APPROVAL: Item Submitted - clarify Strength "as Hydrochloride"

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Zantac®

NDA Number: 18-703

NDA Drug Name: Zantac® (Ranitidine Tablets USP)

NDA Firm: Glaxo Wellcome

Date of Approval of NDA Insert and supplement #: 11/27/96 (S-055)

Has this been verified by the MIS system for the NDA? No (system down)

Was this approval based upon an OGD labeling guidance? Yes

If yes, give date of labeling guidance: February 1997

Basis of Approval for the Container Labels: Side-by-sides submitted

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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. USP 23	X		
Is this name different than that used in the Orange Book? O BOOK - RANITIDINE HCL	X		
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			
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	
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	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		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: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Labeling(continued)	Yes	No	N.A.
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?		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?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		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)			
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. Has "very soluble in water" as does the L.G.-RLD has "soluble in water"		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
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. MODEL LABELING - Labeling Guidance revised 2/97 based on approved RLD labeling for Zantac; Glaxo Wellcome, Inc., Revised December 1995; Approved November 27, 1996.

2. Geneva's product is made with Form I ranitidine.

3. The patent for Form I ranitidine expires 7/25/97. The remaining exclusivities are as follows:

   I-116 (11/3/97) - Maintenance of Healing of Erosive Esophagitis

   I-120 (3/29/98) - Maintenance Therapy For Gastric Ulcer Patients At Reduced Dosage After Healing Acute Ulcers

4. The 150 mg tablet container labels have "150 mg" in white print in a black box while the 300 mg tablet has "300 mg" in black print in a white box.

5. Storage/dispensing:

   USP: Preserve in a tight, light-resistant container. No temperature recommendations.

   ANDA: Store at CRT. Store in a dry place, and protect from light. Dispense in a tight, light-resistant container.

   NDA: Store between 15^{0}-30^{0}C (59^{0}-86^{0}F) in a dry place. Protect from light. Replace cap securely after each opening.

6. SCORING:

   Both strengths for both the NDA and the ANDA are unscored.

7. Components/composition:

   All components are listed in the DESCRIPTION section. The list can be found in attachment #2 in the 3/11/94 correspondence in Vol. 1.1.

8. Containers: (CRC info from chemist review # 5)

   ANDA: 150 mg - 60s (CRC), 100s, 500s, 1000s
   300 mg - 30s (CRC), 250s, 1000s

   NDA: 150 mg - 60s, 180s, 500s, 1000s and unit dose of 100
   300 mg - 30s, 250s and unit dose of 100

9. The tablet descriptions are accurate as portrayed in the HOW SUPPLIED section per chemist review # 5.

10. Bio approval sign-off January 31, 1996.

Date of Review: 5/15/97 **Date of Submission: April 24, 1997**

Primary Reviewer: Adolph Vezza **Date:** 5/16/97

/S/

Team Leader: John Grace **Date:** 5/30/97

/S/

cc:

ANDA 74-467
DUP/DIVISION FILE
HFD-613/AVezza for DKonigstein/JGrace (no cc)
njg/5/16/97¦X:\NEW\FIRMSAM\GENEVA\LTRS&REV\74467.APL
Review

RECORD OF TELEPHONE CONVERSATION

re: New FPL insert labeling needed and need labeling with 3-13-97 amendment for new container closures

I phoned Beth Brannan to communicate a request for new FPL needed before full approval later in the year.

I advised her of changes briefly and stated I would like to fax a copy of our revised guidance which incorporates everything. Further, I would enclose the highlights and directions in a separate cover note.

I also took this opportunity to remind her that two further exclusivities will expire post-approval. The insert should be revised with each exclusivity expiration. A supplement should be forwarded perhaps 30-60 days prior to each expiration. I recommended they not order large quantities, as well.

She expressed she liked the Office's new quick notification process and appreciated the reminder of the exclusivities and tip not to order a lot.

Typically, she said, with a TA, the final minor amendment is submitted ~90 days shy of full approval date, which is 4-25-97 in this case. Do I want a separate labeling amendment? I replied that was up to her.

I also intended to mention the 3-13-97 amendment - they added additional container/closure sizes but this amendment did not contain any labeling. I called her back and left a voice-mail message stating container labels should be submitted and that the HOW SUPPLIED section should be revised to reflect the added container sizes. - if they submit to correct them.

DATE 4-3-97

ANDA NUMBER
74-467

PRODUCT NAME

Ranitidine Tablets

FIRM NAME -
Geneva

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Beth Brannan

TELEPHONE NUMBER

303-466-2400

SIGNATURE

/S/

David Konigstein,
Labeling Reviewer

4-3-97

X:\NEW\FIRMSAM\GENEVA\TELECONS\74467.01L

I noted while glancing through the [illegible] a couple of times

ANDA 74-467 Geneva Pharmaceuticals, Inc.

Ranitidine Tablets USP, 150 mg and 300 mg

Upon further review of this drug product's insert labeling and due to changes in the approved package insert labeling of the reference listed drug, Zantac® (Glaxo Wellcome, Inc.; Approved 11-27-96; Revised December 1995), we have revised our labeling guidance (Revised 2/97).

Briefly, the highlights of the revisions are the following:

1. "Ranitidine" rather than should be used throughout the text, except in the DESCRIPTION section.

2. DESCRIPTION - Chemical name shored up per USP 23 monograph. Note italics, hyphens, and capitals. There should be no spaces.

3. CLINICAL PHARMACOLOGY

   Clinical Trials

   a. Active Duodenal Ulcer, last paragraph - Delete the last sentence

   b. Gastroesophageal Reflux Disease (GERD) - Additional text added as a new last paragraph. ("In two additional ... severity of heartburn.")

4. INDICATIONS AND USAGE

   Item 5. Treatment of GERD - Revise to read "... occurs within 24 hours after starting ..." ["24 hours" rather than "1 or 2 weeks"].

Please revise your insert labeling to be in accordance with the accompanying revised labeling guidance. Submit 12 copies of final printed insert labeling as an amendment to your tentatively approved application. The amendment should be designated as a "MINOR AMENDMENT" in your cover letter.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last insert, with all differences annotated and explained.

If you have any questions or concerns regarding this labeling matter, please contact David Konigstein, Labeling Reviewer, at 301-594-0365.

RECORD OF TELEPHONE CONVERSATION

Ann Bryant called and asked if we could fax a copy of the most recently approved labeling for ranitidine. I said no and that she would have to go through FOI. She said she needed it quicker than FOI could get it to her. I said I could not. She requested to speak to Jerry Phillips. She did and he told her the same thing. Then she called back again on 11/9/95 wanting to know why we requested changes in her FPL labeling. I explained the GATT extension affected one of the exclusivities and would now need to be put into the labeling. She said ok.

DATE
11/8/95

ANDA NUMBER
74-467

IND NUMBER

TELECON

INITIATED BY
X **APPLICANT/ SPONSOR**

FDA

MADE
_X **BY TELE.**

_ **IN PERSON**

PRODUCT NAME
Ranitidine Tablets

FIRM NAME
Geneva

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Ann Bryant

TELEPHONE NUMBER
(303) 438-4292

SIGNATURE
/S/

Geneva Pharmaceuticals, Inc. Reviewer: F. Nouravarsani
Ranitidine HCl Tablets
300 mg
ANDA #74-467
Submission Date:
February 24, 1995

FILE

Beth Brannan, Director
Drug Regulatory Affairs
Phone: (303) 466-2400

1. Reports of the statistical data analysis, GLM Procedure, including 26 subjects was not submitted.

2. The firm was requested to submit a table including **all** original values together with reassayed, values which were used in the study, reason for reassaying, and rationale for the values used. The firm did not submit all of the original values.

9/13/95
Sd/ B...

10-11-95 !
Sue PANOSIAN:
was called and the above DATA
was requested
10-11-95

LABELING REVIEW WORKSHEET

FIRM: **Geneva Pharmaceuticals, Inc.** ANDA: **74-467**
DRUG: **Ranitidine Tablets USP, 150 mg and 300 mg**

LABELING OF THE LISTED DRUG

FIRM: Glaxo Pharmaceuticals and the Labeling Guidance for Ranitidine Tablets USP, Rev. 11/93 NDA# 18-703
APPROVAL DATE: March 29, 1995 REV.DATE: March 1995

CONTAINER LABELS

APPROVED COPY ON FILE? **No**
USP CONTAINER/CLOSURE REQUIREMENTS: **Preserve in a tight, light-resistant container. No temperature recommendations.**
RECOMMENDED STORAGE STATEMENT:
ANDA: **Store at CRT. Store in a dry place, and protect from light. Dispense in a tight, light-resistant container.**
NDA: **Store between 15°-30°C (59°-86°F) in a dry place. Protect from light. Replace cap securely after each opening.**
OTHER KEY ISSUES: **The June 8, 1995 submission contains container labels for the 1000s container size. In the previous submission the firm had submitted container labels for package sizes of 30's, 100's and 500's (150 mg) and 30's, 250's (300 mg). The firm stated the 1000s are the only package size they intend to distribute. (See page 6 in June 8, 1995 Amendment)**

INSERT LABELING

PATENT & EXCLUSIVITY ISSUES: a. The patent for Form I, patent (4128658), expires on July 25, 1997 (This has been extended by GATT from December 5, 1995). Due to this extension the insert labeling ~~needs to~~ has to be updated to include the indication for Alternative Dosage of 300 mg once daily after the evening meal . Form II, patent (4521431), expires on June 4, 2002.

b. Patent # 5028432 is a patent for the gelatin capsule formulation entitled Pharmaceutical capsules containing ranitidine . This patent expires on July 2, 2008. Patent 4880636 expires on May 13, 2008. Patent 4585790 expires May 11, 2004 (extended by GATT from 4/29/2003) and patent 5102665 expires June 23, 2009 (extended by GATT from 4/7/2009).

c. Exclusivity for I-75 (Treatment of Endoscopically Diagnosed Erosive Esophagitis) expires on May 19, 1995.

d. Exclusivity for D-21 (Alternative Dosage of 300 mg once daily after the evening meal) expires on February 28, 1997.

e. Exclusivity for I-116 (Maintenance of Healing of Erosive Esophagitis) expires on November 3, 1997.

f. Because the exclusivity for Form 1 expires on July 25, 1997, the indication for Alternative Dosage of 300 mg daily after the evening meal will now be included in the labeling. The indications for Maintenance of Healing of Erosive Esophagitis and Maintenance Therapy for Gastric Ulcer

EXCLUSIVITY STATEMENT

According to information published in the list of Approved Drug Products 17th Ed.,

Supplement 4, Zantac® Tablets are entitled to a period of mardeting exclusivity for:

I-116	Maintenance of healing of erosive Esophagitis	Expires: November 3, 1997
I-120	Maintenance and therapy for gastric ulcer patients at reduced dosage after healing acute ulcers	Expires: March 29, 1998

GENEVA PHARMACEUTICALS, INC

Beth Brannan, Director
Drug Regulatory Affairs

8/29/97
Date

CERTIFICATION OF SUBMISSION OF FIELD COPY

In accordance with 21 CFR 314.96(b) (September 8, 1993 **Federal Register** Final Rule Notice), Geneva Pharmaceuticals, Inc. hereby certifies that a field copy of required information from our amendment to our Abbreviated New Drug Application for Ranitidine Tablets, USP, 150 mg and 300 mg has been provided to the Denver District office, FDA.

In addition, we hereby certify that the field copy of this amendment is a true copy of the submission to the Office of Generic Drugs.

Beth Brannan

11/22/95

Beth Brannan Date

Director

Drug Regulatory Affairs

REVIEW OF PROFESSIONAL LABELING #3

Orig. Amendment (Major)

FPL - Container labels and Package Insert labeling

DATE OF REVIEW: August 28, 1995

ANDA #: 74-467

NAME OF FIRM: Geneva Pharmaceuticals, Inc.

NAME OF DRUG: Ranitidine Tablets USP, 150 mg and 300 mg

DATE OF SUBMISSION: June 8, 1995

COMMENTS:

CONTAINER: 1000s (150 mg and 300 mg)

Satisfactory. We acknowledge the change in package size.

INSERT:

1. GENERAL COMMENT

   Due to GATT patent extensions your insert labeling should be revised as indicated below. In addition, you should amend your application as appropriate.

2. CLINICAL PHARMACOLOGY

   Clinical Trials, *Erosive Esophagitis* - Revise the subsubsection heading to appear italicized and not in bold print.

3. INDICATIONS AND USAGE

   Revise the sixth indication to read as follows:

   Treatment of endoscopically diagnosed erosive esophagitis. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with ranitidine 150 mg qid.

4. ADVERSE REACTIONS

   Integumentary - Revise to read:

   ...cases of erythema multiforme, and rarely, alopecia.

5. DOSAGE AND ADMINISTRATION

a. Active Duodenal Ulcer - Revise paragraph 1 to read:

...daily. An alternative dosage of 300 mg once daily after the evening meal or at bedtime can be used for patients in whom...

b. Maintenance Therapy - Revise this subsection heading to read:

Maintenance of Healing of Duodenal Ulcers

6. HOW SUPPLIED

We encourage you to list the NDC numbers in this section.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their package insert labeling, then prepare and submit final printed insert labeling. Please note that final printed insert labeling is not required for tentative approval of an application if it is granted with more than 90 days remaining from the date when full approval can be considered. We will accept final "printers proof" for the insert only. Should further information become available relating to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

NOTE TO THE CHEMIST:

1. Please note that the firm has changed their package sizes as follows: Accelerated stab is ...

a) 150 mg (1000's) rather than (30's, 100's and 500's 60's).

b) 300 mg (1000's), rather than (250's and 1000's).

2. The firm has changed the shape of the 300 mg tablet from a "modified capsule" to a "round tablet". Is this acceptable?

Q "Comparative Dissolution Profi... submitted dated 6/7/95. Acce... 8/95

FOR THE RECORD:

1. This review was based on the labeling guidance for Ranitidine Tablets USP (Revised November 1993) and new labeling of the listed drug Zantac® (Glaxo; Approved March 29, 1995; Revised March 1995).

2. The firm has submitted a second ranitidine application which is titled Form II (ANDA 74-232), this application is Form I. Form I is a granular substance that is soluble in water. Form II is a crystalline substance that is very soluble in water. (See Description section).

3. Patents/Exclusivity:

   a. The patent for Form I, patent (4128658), expires on July 25, 1997 (This has been extended by GATT from December 5, 1995). Due to this extension the insert labeling needs to be updated to include the indication for "Alternative Dosage of 300 mg once daily after the evening meal". Form II, patent (4521431), expires on June 4, 2002.

   b. Patent # 5028432 is a patent for the gelatin capsule formulation entitled "Pharmaceutical capsules containing ranitidine". This patent expires on July 2, 2008. Patent 4880636 expires on May 13, 2008. Patent 4585790 expires May 11, 2004 (extended by GATT from 4/29/2003) and patent 5102665 expires June 23, 2009 (extended by GATT from 4/7/2009).

   c. Exclusivity for I-75 (Treatment of Endoscopically Diagnosed Erosive Esophagitis) expired on May 19, 1995.

   d. Exclusivity for D-21 (Alternative Dosage of 300 mg once daily after the evening meal) expires on February 28, 1997.

   e. Exclusivity for I-116 (Maintenance of Healing of Erosive Esophagitis) expires on November 3, 1997.

   f. Because the exclusivity for Form 1 expires on July 25, 1997, the indication for Alternative Dosage of 300 mg daily after the evening meal will now be included in the labeling. The indications for Maintenance of Healing of Erosive Esophagitis and Maintenance Therapy for Gastric Ulcer Patients at Reduced Dosage After Healing Acute Ulcers, will not be contained in the insert labeling of this ANDA because they expire post July 25, 1997.

4. Storage and Dispensing:

USP: Preserve in a tight, light-resistant container. No temperature recommendations.

NDA: Store between 15°-30° (59°-86°F) in a dry place. Protect from light. Replace cap securely after each opening.

ANDA: Store at CRT 15°-30°C (59°-86°F). Store in a dry place, and protect from light. Dispense in a tight, light-resistant container.

5. Scoring:

NDA: Both strengths unscored.

ANDA: Both strengths unscored.

6. Components/Composition:

All components are listed in the DESCRIPTION section. The list can be found in attachment #2 in the 3/11/94 correspondence in Vol. 1.1.

7. The firm states that they intend to market a container of 1000 only. See page 6 of response from firm in the June 8, 1995 amendment. See NOTE TO THE CHEMIST.

8. The established name should read "Ranitidine Tablets USP" rather than "Ranitidine Hydrochloride Tablets". The USP uses Ranitidine Hydrochloride as the compound and Ranitidine Tablets as the finished dosage form. This differs from the innovator's title.

9. The firm has revised the shape of the 300 mg tablet from a "modified capsule" to a "round tablet". See response from firm on page 7 in the June 8, 1995 amendment. See NOTE TO CHEMIST.

Carol Zimmermann

/S/ 9/15/95

cc: ANDA 74-467
HFD-613/CZimmermann/AVezza/CHoppes (no cc)
caz 8/28/95
74467JUN.95

/S/ 9/15/95

REVIEW OF PROFESSIONAL LABELING #2

Orig. Amendment (Major)

DRAFT - Package insert labeling and FPL - Container labels

DATE OF REVIEW: February 7, 1995

ANDA #: 74-467 NAME OF FIRM: Geneva Pharmaceuticals, Inc.

NAME OF DRUG: Ranitidine Tablets USP, 150 mg and 300 mg

DATE OF SUBMISSION: November 11, 1994

COMMENTS:

CONTAINER: 30's, 100's, 500's (150 mg) and 30's, 250's (300 mg)

Satisfactory. We acknowledge the change in package sizes.

INSERT:

1. GENERAL COMMENT

   Please increase the readability of the text in your insert. It is difficult to read in some areas.

2. PRECAUTIONS

   Pediatric Use - Revise as follows:

   ...in pediatric patients have...

3. ADVERSE REACTIONS

   Integumentary - Revise as follows:

   ...cases of erythema...

4. OVERDOSAGE

   Paragraph 3, line 1 - Revise so that "mg/kg" appear on the same line.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their package insert labeling, then prepare and submit final printed insert labeling. Please note that final printed insert labeling is not

required for tentative approval of an application if it is granted with more than 90 days remaining from the date when full approval can be considered. We will accept final "printers proof" for the insert only. Should further information become available relating to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

NOTE TO THE CHEMIST:

1. The firm has stated in their communication dated November 11, 1994, that they will comply with the Poison Prevention Packaging Act regarding child-resistant closures. However, the data submitted contains a 60 unit fill bottle and no 30 unit fill bottle. The company is not planning to manufacture a 60 tablet container. Will this data be adequate to ensure a CRC closure on the 30's package size?

   The subject will be issue with the concept to applicant. Data is More needed. E. Parrot 3/1/95

2. Please note that the Firm has changed their package sizes as follows:

   a) 150 mg (30's, 100's, 500's) rather than (60's and 1000's claimed as previously

   b) 300 mg (250's rather than the 1000's), the 30's were retained.

FOR THE RECORD:

1. This review was based on the labeling guidance for Ranitidine Tablets USP (Revised November 1993) and new labeling of the listed drug Zantac® (Glaxo; Approved November 10, 1994; Revised September 1994).

2. The firm has submitted a second ranitidine application which is titled Form II (ANDA 74-232), this application is Form I. Form I is a granular substance that is soluble in water. Form II is a crystalline substance that is very soluble in water. (See Description section).

3. Patents/Exclusivity:

   a. The patent for Form I, patent (4128658), expires on December 5, 1995. Form II, patent (4521431), expires on June 4, 2002.

b. Patent # 5028432 is a patent for the gelatin capsule formulation entitled "Pharmaceutical capsules containing ranitidine". This patent expires on July 2, 2008.

c. Exclusivity for I-75 (Treatment of Endoscopically Diagnosed Erosive Esophagitis) expires on May 19, 1995.

d. Exclusivity for D-21 (Alternative Dosage of 300 mg once daily after the evening meal) expires on February 28, 1997.

e. Exclusivity for the indication of Healing Erosive Esophagitis approved on November 3, 1994, will get exclusivity until 11/3/97. See E-Mail dated 2/16/95, from Mary Ann Holovac.

f. Because the exclusivity for Form 1 expires in 1995, the indication for Alternative Dosage of 300 mg daily after the evening meal and Healing Erosive Esophagitis, which both expire in 1997, will not be contained in the insert labeling of this ANDA.

4. Storage and Dispensing:

USP: Preserve in a tight, light-resistant container. No temperature recommendations.

NDA: Store between 15°-30° (59°-86°F) in a dry place. Protect from light. Replace cap securely after each opening.

ANDA: Store at CRT 15°-30°C (59°-86°F). Store in a dry place, and protect from light. Dispense in a tight, light-resistant container.

5. Scoring:

NDA: Both strengths unscored.

ANDA: Both strengths unscored.

6. Components/Composition:

All components are listed in the DESCRIPTION section. The list can be found in attachment #2 in the 3/11/94 correspondence in Vol. 1.1.

7. The firm states that they will package the 30 size bottle in a CRC cap. See NOTE TO THE CHEMIST #1

8. The established name should read "Ranitidine Tablets USP" rather than "Ranitidine Hydrochloride Tablets". The USP uses Ranitidine Hydrochloride as the compound and Ranitidine Tablets as the finish dosage form. This differs from the innovators title.

Carol Zimmermann

cc: ANDA 74-467
HFD-613/CZimmermann\APayne\JPhillips (no cc)
mpd/2/23/95; (95) 74467NOV.94
Review
final

/S/ 2/24/95

/S/ 2/24/95

RECORD OF TELEPHONE CONVERSATION

Ranitidine Tablets 74-467

Jennifer Hutchinson of Geneva phoned and asked me to check the information they submitted for their Paragraph IV certification to see if the letter from Geneva notifying Glaxo of their intentions. She indicated that the submission was dated March 11, 1994.

I requested the ANDA from the document room and looked at the referenced submission. It did not contain the notification to Glaxo.

I phoned Jennifer Hutichinson and informed her that the infomation was not with the submission.

She Indicated that she would send an amendment to include this information.

DATE
March 21, 1994

ANDA NUMBER
74-467

IND NUMBER

TELECON

INITIATED BY MADE

X **APPLICANT/**
X **BY SPONSOR**
TELE.

FDA _ **IN PERSON**

PRODUCT NAME
Ranitidine Tablets 150 mg and 300 mg

FIRM NAME
Geneva

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Jennifer Hutchinson

TELEPHONE NUMBER
303-466-2400

SIGNATURE
Cecelia M. Parise

/S/

REVIEW OF PROFESSIONAL LABELING #1

ANDA

DRAFT

DATE OF REVIEW: May 23, 1994

ANDA 74-467

NAME OF FIRM: Geneva Pharmaceuticals, Inc.

NAME OF DRUG: Ranitidine Tablets USP, 150 mg and 300 mg

DATE OF SUBMISSION: February 16, 1994

COMMENTS:

Container:

1. Please assure the prominence of the product name and strength.

2. Capitalize the "P" and "I" that appears in the company name on the main panel.

3. The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). Your proposed container of 30 (300 mg) and 60 (150 mg) appear to be in this category. We believe that these packages should comply with the Act. Please comment.

4. Please differentiate between your two product strengths by the use of boxing, contrast colors, or some other means.

Insert:

1. GENERAL COMMENT

   Please be consistent with where you begin the text following a section heading.

2. DESCRIPTION

   a. Paragraph 1, Line 3 - "hydrochloride" rather than

3. CLINICAL PHARMACOLOGY

a. Pharmacokinetics

i. Paragraph 2 - "(150 mmol)" rather than

ii. Paragraph 4, Line 6 - "ranitidine intravenously" rather than

iii. Clinical Trials

(1). Maintenance Therapy in Duodenal Ulcer (Table 3) - Revise the fourth column to read: No. of Patients.

(2). Gastric Ulcer

Paragraph 2 - "...ranitidine hydrochloride...".

(3). Gastroesophageal...

(a) Paragraph 1, Line 3 - ....ranitidine 150 mg bid was more...

(b) Paragraph 2, Line 1 - "...ranitidine 150 mg bid..."

(c) Paragraph 2, Line 2 - "...1 to 2 weeks..." rather than

(d) Delete the last paragraph.

(e) Add the following paragraph and table as the final subsection:

Erosive Esophagitis: In two multicenter, double-blind, randomized, placebo-controlled, 12-week trials performed in the United States, ranitidine 150 mg qid was significantly more effective than placebo in healing endoscopically-diagnosed erosive esophagitis and in relieving

associated heartburn. The erosive esophagitis healing rates were as follows:

EROSIVE ESOPHAGITIS PATIENT HEALING RATES

	Healed/Evaluable	
	Placebo*	Ranitidine HCL 150 mg qid*
	n=229	n=215
Week 4	43/198 (22%)	96/206 (47%)
Week 8	63/176 (36%)	142/200 (71%)
Week 12	92/159 (58%)	162/192 (84%)

*All patients were permitted p.r.n. antacids for relief of pain.
+p< 0.001 versus placebo.

No additional benefit in healing of esophagitis or in relief of heartburn was seen with a ranitidine dose of 300 mg qid.

4. INDICATIONS AND USAGE

a. Item 5 - Revise as follows:

...starting therapy with rantidine 150 mg bid. (Delete the second sentence).

b. Add the following as item 6:

Treatment of endoscopically-diagnosed erosive esophagitis. Healing of endoscopically-diagnosed erosive esophagitis occurs at 4 weeks (47%), 8 weeks (71%), and 12 weeks (84%) of therapy with ranitidine 150 mg qid. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with ranitidine.

c. Revise the last paragraph to read as follows:

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; GERD; and erosive esophagitis.

5. CONTRAINDICATIONS

Revise as follows:

Ranitidine is contraindicated in patients... drug or any of the ingredients...

6. PRECAUTIONS

a. Add the following as item 3 of the General subsection:

Rare reports suggest that ranitidine may precipitate acute porphyric attacks in patients with acute porphyria. Ranitidine should therefore be avoided in patients with a history of acute porphyria.

b. Drug Interactions

The third sentence should begin the second paragraph.

c. Your subsection headings should be of the same prominence as seen in your other sections.

7. ADVERSE REACTIONS

a. Hepatic, line 3 - "intravenously" rather than (appears twice).

b. Musculoskeletal - "...arthralgias and myalgias."

8. DOSAGE AND ADMINISTRATION

Insert the following below the GERD subsection.

Erosive Esophagitis: The current recommended adult oral dosage is 150 mg four times a day.

9. HOW SUPPLIED

a. Line 1, - Ranitidine Tablets USP, for oral...

b. Please indicate that the tablets are unscored.

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 final printed container labels and draft insert labeling.

NOTE TO THE CHEMIST:

Please confirm whether the 30 and 60 tablets package size have CRC. If the answer is yes, I will delete comment 43 under container.

43 per A Payne Worklist 6/13/94

FOR THE RECORD

1. Review based on the labeling guidance(Revised Nov. 1993) for the listed drug (Zantac; Glaxo; Approved April 5, 1993; Revised July 1992).

2. It appears that the firm has submitted a second ranitidine application which is titled Form I (ANDA 74-467) which differs from another application Form II (ANDA 74-232). Form I is a granular substance that is soluble in water. Form two is a crystalline substance that is very soluble in water. (See DESCRIPTION section).

3. Exclusivity for I-75 (Treatment Of Endoscopically Diagnosed Erosive Esophagitis expires on May 19, 1995).

4. Patent (4128658) expires Dec.05, 1995 for form I.

5. Storage/Dispensing

   ANDA: CRT, store in a dry place and protect from light. Replace cap securely after each opening.
   Dispense in a tight, light-resistant container.

   NDA: Store between 15°-30°C (59°- 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

   USP: Preserve in tight, light-resistant containers.

6. Neither the NDA nor ANDA products are scored.

Angela Payne

MEMO TO THE RECORD

The firm currently has an application on file for Ranitidine Hydrochloride Tablets. The pending application utilizes Type II ranitidine HCl. Type II ranitidine has patent protection until June 4, 2002. The proposed application (74-467) uses Type I ranitidine HCl as the NDS. The firm has submitted a paragraph IV certification with this ANDA.

A meeting was held on March 7, 1994, to discuss the acceptability of two ANDAs for the same drug product held by a single applicant. Dr. Guyer, Florence Fang, Cecelia Parise, Don Hare, Shari Sheehan, Justina Molzon, Bob Pollock, and Gordon Johnston were in attendance.

The regulations do not permit an applicant to file a second application for the same drug product if it already the subject of an **approved** application. In this case, Geneva's ANDA utilizing Type II ranitidine is unapproved. The proposed ANDA (Type I ranitidine) requires manufacturing procedures and controls that are substantially different from those used in the manufacture of the Type II product. Because of these differences in manufacturing and controls, the information would not be permitted in a single application. Thus, based on the above issues it was determined that an application would be filed for Type I ranitidine.

/S/ 3/8/94

Gordon Johnston

CERTIFICATION OF SUBMISSION OF FIELD COPY

In accordance with 21 CFR 314.96(b) (September 8, 1993 Federal Register Final Rule Notice), Geneva Pharmaceuticals, Inc. hereby certifies that a field copy of required information for the ANDA 74-467 Ranitidine Tablets USP, 150 mg and 300 mg amendment has been provided to the Denver district office.

In addition, we hereby certify that the field copy of this amendment is a true copy of the technical section described in 21 CFR 314.94(a)(9).

Beth Brannan 3/2/94

Beth Brannan Date

Director

Drug Regulatory Affairs

RECORD OF TELEPHONE CONVERSATION

I contacted Jennifer Hutchinson at Geneva to ask that they revise the second paragraph on the third copy certification. The word amendment was inserted in place of application.

In addition, I requested that they send one more copy of the draft labeling. The application contained three copies instead of four.

DATE
March 2, 1994

ANDA NUMBER
74-467

IND NUMBER

TELECON

INITIATED BY	MADE
_ APPLICANT/ SPONSOR	X BY TELE.
X FDA	_ IN PERSON

PRODUCT NAME
Ranitidine Tablets, 150 mg and 300 mg

FIRM NAME
Geneva

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Jennifer Hutchinson Regulatory Affairs

TELEPHONE NUMBER
303-466-2400

SIGNATURE
Cecelia M. Parise

/S/

File: 74-467

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : February 23, 1994

TO : Director
Division of Bioequivalence (HFD-650) /S/

FROM : Chief, Regulatory Support Staff
Office of Generic Drugs (HFD-632) 2/24/94

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Ranitidine Tablets USP, 150 mg and 300 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355(4)(B)(iv).

Geneva Pharmaceuticals, Inc. has submitted an ANDA for Ranitidine Tablets. The ANDA contains a certification pursuant to 21 USC 355(j)(2)(A)(vii)(iv) stating that a patent expiring June 4, 2002, will not be infringed by the manufacture or sale of the proposed product. In order to accept an ANDA for filing that contains such a patent certification, the Agency must formally make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the study submitted by Geneva Pharmaceuticals, Inc. on February 16, 1994, for its Ranitidine product satisfies the statutory requirements of "completeness" so that the ANDA may be filed and that a period of six months of market exclusivity can be granted to the applicant who submitted the first substantially complete ANDA under 21 USC 355(j)(4)(B)(iv).

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

✓ Study meets statutory requirements

_____ Study does **NOT** meet statutory requirements

Reason:

/S/ 2/25/94

Director, Division of Bioequivalence Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74467

CORRESPONDENCE

ANDA 74-467

Geneva Pharmaceuticals, Inc.
Attention: Ms. Beth Brannan
2555 W. Midway Blvd.
P. O. Box 446
Broomfield, Colorado 80038-0446

MAR 17 1995

Dear Ms. Brannan:

This is in reference to your abbreviated new drug application dated February 16, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ranitidine Hydrochloride Tablets, USP, 150 mg and 300 mg.

Reference is also made to your amendment dated November 11, 1994.

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

A. Chemistry Deficiencies

1. A description of the container configuration to be used to store the dried granulation and the coated tablets should be provided. Also, specify if a desiccant bag will be used. Be aware that the computation of the expiration date should be based from the initial compounding of two ingredients and not from the completion date of the coating process.

2. We recommend that further studies be conducted in order to determine if physical interconversion is occurring during the course of granulating the subject drug product. We propose that a sample of Ranitidine Hydrochloride Form I working standard be diluted in -- evaporated, then test the residues using The spectra obtained should be provided.

3. The coating solution's "total solids" percentage should be provided.

4. Your finished drug product release specifications submitted in attachment 7, of your letter dated 11/11/94, to reflect the revised "Related Compounds" specifications does not harmonize with the proposed specifications submitted in response to deficiency No. 16, page 6, of the subject letter. These specifications should be tightened to reflect the data

obtained for releasing lot Nos. 6494065 and 6494066. Also, your Related Compounds stability specification should be revised according to the data obtained throughout the accelerated stability studies. Please provide revised release and stability specifications for the subject test methods.

5. Your intended marketing container configurations for the subject drug products have been changed. According to the labeling submitted, you are proposing to distribute the 150 mg dosage form in 30's, 100's and 500's rather than the 60's and 1,000's; the 300 mg dosage form in 250's rather than the 1,000's. These are substantially different from the originally proposed container configurations. We recommend that you provide accelerated stability studies data gathered in the smallest/largest of the now proposed container configurations and include a revised "Master Packaging Specification" form. Please be aware that information pertaining to the proposed container/closure systems must be filed in the container section of your application.

B. Labeling Deficiencies

CONTAINER: 30's, 100's, 500's (150 mg) and 30's, 250's (300 mg)

Satisfactory. We acknowledge the change in package sizes.

INSERT:

1. GENERAL COMMENT

   Please increase the readability of the text in your insert. It is difficult to read in some areas.

2. PRECAUTIONS

   Pediatric Use - Revise as follows:

   ...in pediatric patients have...

3. ADVERSE REACTIONS

   Integumentary - Revise as follows:

   ...cases of erythema...

4. OVERDOSAGE

   Paragraph 3, line 1 - Revise so that "mg/kg" appear on the same line.

Please revise your package insert labeling, then prepare and submit final printed insert labeling. Please note that final printed insert labeling is not

The file 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/ 3/16/95

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

ANDA 74-467

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

MAR 8 1994

Dear 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: Ranitidine Tablets USP, 150 mg and 300 mg

DATE OF APPLICATION: February 16, 1994

DATE OF RECEIPT: February 17, 1994

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

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

Sincerely yours,

/S/ 3/8/94

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA#74-467
DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsements:
HFD-615/Gordon Johnston, Chief 3/8/94 /date/
HFD-615/PRickman, CSO date/3/1/94
HFD-615/WRussell, ~~CSO~~ date/3/7/94
HFD-645/BArnwine (BJ 3/8/94
WP File\russell\74-467
F/T by bcw/3-7-94
ANDA Acknowledgement Letter!

1.1

B G

Ranitidine Hydrochloride Tablets, USP
ANDA 74-467

Geneva Pharmaceuticals Inc.
Attention: Ms. Beth Brannan
2555 W. Midway Blvd.
Post Office Box 446
Broomfield, CO 80038-0446

JAN 9

Dear Ms. Brannan:

Reference is made to the *in vivo* bioequivalence study, *in vitro* dissolution data and waiver request submitted February 16, 1994, for Ranitidine Hydrochloride Tablets USP, 300 mg and 150 mg.

The Office of Generic Drugs has reviewed the referenced material and has found the bioequivalence study comparing the test product, ranitidine hydrochloride tablets, 300 mg, lot #6493066, with the reference listed drug, Zantac Tablets, 300 mg, to be incomplete for the following reasons:

1. All of the assayed data was not analyzed statistically.

   The study protocol (No. 930825) states in pertinent part "24 healthy adult male volunteers and 2 alternates will be enrolled. Samples from subjects No. 1-24 will be analyzed if the subjects complete the study." The study report notes that samples from all 26 subjects were assayed by error.

   The use of 24 subjects in the statistical analysis may have been acceptable, before the samples were assayed, however once the samples are assayed, the Office must be assured that there are no biases in selecting 24 of the 26 subjects. Since the samples from all 26 subjects were analyzed, data from all 26 subjects should be statistically analyzed and will be required to satisfy bioequivalence criterion. Please reanalyze the data using all 26 subjects and submit this information for review.

2. The limit of quantification (LOQ) of ng/mL is too low.

   Significant interference was observed for the following subject samples:

The LOQ should be increased in the future.

3. All original values should be reported together with reassayed values which were used in the study and reason for reassaying, and rationale for the used values should be reported and summarized in a table.

   For example the original values for the following samples should be reported:

4. The waiver request for bioequivalence study requirements for the 150 mg product may not be granted at this time. The waiver request should be resubmitted with the amendment.

5. It was stated that samples will be stored frozen until May 25, 1994, and then discarded. The samples were stored less than one year, the clinical study was started on October 8, 1993. In future studies the storage period should be increased to at least one year.

You are required to take an action described under 21 CFR 314.96 which will amend this application.

If you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

for

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

4.1

ANDA 74-467

JUN 18 1997

Geneva Pharmaceuticals, Inc.
Beth Brannan
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ranitidine Tablets USP.

This letter addresses issues related to the 180-day exclusivity provisions under section 505(j)(4)(B)(iv) of the Act.

The listed drug product referenced in your application is subject to periods of patent protection which expire on July 25, 1997, (patent 4,128,658) and June 4, 2002, (patent 4,521,431).

The Agency has reviewed the application of the 180-day exclusivity provisions of the Act to the ANDAs submitted for ranitidine. FDA's regulations interpreting these provisions are set out at 21 CFR 314.107(c). The U.S. District Court for the District of Columbia has recently held that the Agency's interpretation of the 180-day exclusivity provisions is inconsistent with the Act, and found invalid the Agency's position that in order to qualify for 180 days of exclusivity the first ANDA applicant with a paragraph IV certification must be sued and prevail in patent infringement litigation. Mova Pharmaceuticals v. Kessler, 955 F. Supp. 128 (D.D.C. 1997). See also Inwood Laboratories, Inc. v. Young, 723 F. Supp. 1523 (D.D.C. 1989), vacated as moot, 43 F.3d 712 (D.C. Cir. 1989). The court determined that the Act requires exclusivity be granted to the first ANDA submitted with a paragraph IV certification to a patent, regardless of whether such certification results in litigation or whether the applicant prevails in the litigation. Until such time as the decision is reversed on appeal, FDA will acquiesce in the Mova decision.

In the case of approval of ANDAs for ranitidine, Mova dictates that Genpharm Inc., the first ANDA applicant with a paragraph IV

certification to the patents listed for the reference drug, receive 180 days of exclusivity. The Act [21 U.S.C. § 355(j)(4)(B)(iv)] provides that a subsequent application shall be made effective not earlier than one hundred and eighty days after:

> (I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or
>
> (II) the date of a decision of a court in action described in clause [505(j)(4)(b)(iii)] holding the patent which is the subject of the certification to be invalid or not infringed, whichever is earlier.

The Agency interprets this provision as triggering the beginning of the 180 day exclusivity period with a decision of <u>any</u> court in a patent infringement action related to a paragraph IV certification finding the patent invalid or not infringed, whether or not it is the court hearing a patent infringement action resulting from the first paragraph IV certification.

The first decision of a court in an action resulting from a paragraph IV certification to a patent listed for ranitidine holding the patent invalid or not infringed has been rendered. In that case, the District Court for Connecticut granted Boehringer-Ingelheim partial summary judgement on October 7, 1996, finding that the Boehringer-Ingelheim product (Form I) does not infringe the Form II patent (patent 4,521,431). The court ruled on other claims in the case on November 18, 1996. Final judgement was entered on January 31, 1997.

FDA regulations describe that the 180-day period will begin running from "the date of a decision of the court holding the relevant patent invalid, unenforceable, or not infringed." 21 CFR 314.107(c)(1)(ii). The relevant date of final decision of a court on patent issues is defined in 21 CFR 314.107(e)(2)(I) as follows:

> If the district court enters a decision that the patent is invalid, unenforceable, or not infringed, and the decision is not appealed, the date on which the right to appeal lapses.

In the case involving Boehringer-Ingelheim, the right to appeal did not lapse until March 3, 1997. Glaxo did not appeal the October 7, 1996 ruling. The 180 day period began on March 3, 1997, and will expire on August 29, 1997. It is important to note that the FDA will not approve an ANDA prior to the expiration of exclusivity notwithstanding a licensing agreement. This is explained in the preamble to the final rule, where the

Agency states that licensees are subject to the 180-day exclusivity period [59 Fed. Reg. 50338, 50346, 50353 (Oct.3, 1994)]. Therefore, final approval cannot be granted until August 29, 1997.

If you have any questions concerning this matter, please feel free to contact Mr. Peter Rickman, Chief, Regulatory Support Branch at (301) 827-5862.

Sincerely yours,

/S/

for 6/18/97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-467

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ranitidine Tablets USP, 150 mg and 300 mg (present as the hydrochloride).

As you may be aware, the U.S. Food and Drug Administration has recently been involved in litigation with a number of generic pharmaceutical companies over the final approval date for abbreviated new drug applications (ANDAs) for ranitidine hydrochloride tablets (Glaxo's ZANTAC). This letter is intended to provide you with an update on the Office of Generic Drugs' plans for approval of ranitidine hydrochloride ANDAs in light of the litigation.

In mid June, 1997, FDA sent letters to a number of applicants with pending ANDAs for ranitidine hydrochloride, informing them that the agency would acquiesce in Mova Pharmaceuticals v. Kessler, 955 F.Supp. 128 (D.D.C. 1997), and therefore would grant Genpharm, Inc. 180 days of exclusivity as the first ANDA for ranitidine hydrochloride with a paragraph IV certification. Genpharm's exclusivity was calculated to begin on March 3, 1997, and to expire on August 29, 1997. ANDAs for ranitidine hydrochloride could be approved once Genpharm's exclusivity expires.

Granutec Pharmaceuticals, Inc. sued FDA in the U.S. District Court for the Eastern District of North Carolina, claiming that the agency should not acquiesce in the Mova decision, but instead should apply its regulations (21 CFR 314.107(c)) to deny exclusivity to any applicant for generic ranitidine hydrochloride. The district court agreed with Granutec, and on July 3, 1997, entered an order directing FDA to approve the Granutec ANDA on July 10, 1997, pursuant to Granutec's licensing agreement with Glaxo. On July 9, 1997, the United States Court of Appeals for the Fourth Circuit stayed the District Court order.

Because the district court order has been stayed, the agency will proceed as intended prior to the initiation of the litigation.

Under the reasoning of the court in Mova, Genpharm has 180 days of exclusivity, which began on March 3, 1997, and will expire on August 29, 1997.

If you have any questions regarding the effect of this decision on the approval of your application, please contact Kassandra C. Sherrod, Project Manager, at (301) 827-5849 at the Office of Generic Drugs.

Sincerely yours,

/S/

7/15/97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-467

JAN 31 1996

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Boulevard
Broomfield, Colorado 80038-0446

Dear Madam:

Reference is made to your abbreviated new drug application dated February 16, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ranitidine Tablets USP, 150 mg and 300 mg. The application contains certifications under section 505(j)(2)(A)(vii)(III) and (IV) of the Act.

Reference is also made to your amendments dated February 27, October 27, November 22, 1995, and January 22, 1996.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved.** This determination is based upon information available to the Agency at this time, which includes information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug products. Therefore, this determination is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(4)(B)(iv) of the Act.

The listed drug product referenced in your application is subject to a period of patent protection which expires on July 25, 1997, (patent 4,128,658) and June 4, 2002, (patent 4,521,431). However, litigation is underway in the United States District Court for the District of New Jersey involving a challenge to the patent (Glaxo Inc., Glaxo Group Limited, and Allen & Hanburys Limited v. Geneva Pharmaceuticals Inc., Ciba-Geigy Corporation, Interchem Trading Corporation and Union Quimico Farmaceutica S.A., Civil Action Nos. 94-1921 and 94-4589.) Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(4)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

   b. the date of court decision [505(j)(4)(B)(iii) (I), (II), or (III)], which has been interpreted by the Agency to mean the date of the final order or judgement of that court from which no appeal can be or has been taken, or,

   c. the patent has expired (in this case there are two relevant patents to consider), and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the Agency whether circumstances have or have not arisen that may affect the effective date of final approval. Your amendment must provide:

1. a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the district court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

   b. a statement that no such changes have been made to the application since the date of tentative approval.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, these drug products will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

The amendment should be designated as a MINOR AMENDMENT in your cover letter. Before you submit the amendment, please contact Ms. Kassandra C. Sherrod, Consumer Safety Officer, at (301) 594-1300, for further instructions.

Sincerely yours,

/S/ MD 1/31/96

Charles J. Ganley, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

ANDA 74-467
Division File
DUP Jacket
Field Copy
HFD-600/Reading File
HFD-8/P.Savino

Endorsements:

HFD-645/E.Ramos/12/5/95
HFD-645/K.Sherrod/12/7/95
HFD-613/C.Zimmermann 1/3/96
HFD-613/C.Hoppes 1/4/96
HFD-645/B.Arnwine/ 1/31/96

TENTATIVE APPROVAL LETTER

ANDA 74-467

Geneva Pharmaceuticals, Inc.
Attention: Ms. Beth Brannan
2555 W. Midway Blvd.
P. O. Box 446
Broomfield, Colorado 80038-0446

OCT 27 1995

Dear Ms. Brannan:

This is in reference to your abbreviated new drug application dated February 16, 1994, and acceptable for filing on March 8, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ranitidine Tablets, USP, 150 mg and 300 mg.

Reference is also made to your amendment dated June 8, 1995.

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

Chemistry Deficiency

Please revise your 300 mg finished product specification form to reflect the change from to round tablet" shape.

Labeling Deficiencies:

CONTAINER: 1000s (150 mg and 300 mg)

Satisfactory. We acknowledge the change in package size.

INSERT:

1. GENERAL COMMENT

   Due to GATT patent extensions your insert labeling should be revised as indicated below. In addition, you should amend your application as appropriate.

2. CLINICAL PHARMACOLOGY

   Clinical Trials, *Erosive Esophagitis* - Revise the subsubsection heading to appear italicized and not in bold print.

3. INDICATIONS AND USAGE

Revise the sixth indication to read as follows:

Treatment of endoscopically diagnosed erosive esophagitis. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with ranitidine 150 mg qid.

4. ADVERSE REACTIONS

Integumentary - Revise to read:

...cases of erythema multiforme, and rarely, alopecia.

5. DOSAGE AND ADMINISTRATION

a. Active Duodenal Ulcer - Revise paragraph 1 to read:

...daily. An alternative dosage of 300 mg once daily after the evening meal or at bedtime can be used for patients in whom...

b. Maintenance Therapy - Revise this subsection heading to read:

Maintenance of Healing of Duodenal Ulcers

6. HOW SUPPLIED

We encourage you to list the NDC numbers in this section.

Please revise your package insert labeling, then prepare and submit final printed insert labeling. Please note that final printed insert labeling is not required for tentative approval of an application if it is granted with more than 90 days remaining from the date when full approval can be considered. We will accept final "printers proof" for the insert only. Should further information become available relating to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

The file 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/ 10/26/95

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

Geneva pharmaceuticals, inc.

2555 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400 • FAX (303) 466-3717

FEDERAL EXPRESS

24Feb95

BIOAVAILABILITY

Acting Director,
Office of Generic Drugs,
Division of Bioequivalence - HFD-650
Centre for Drug Evaluation and Research,
Metro Park North 2,
7500 Standish Place, Room 150
Rockville, MD 20855

DEV CORRESP

RE: ANDA 74-467 Ranitidine Hydrochloride Tablets USP, 150 mg and 300 mg
Amendment - Bioequivalence Study

Dear Director:

We are submitting an amendment to our unapproved Abbreviated New Drug Application for Ranitidine Hydrochloride Tablets, in accord with Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to your written communication of January 9, 1995.

1. The data has been reanalyzed to include all 26 subjects and the results are provided in Tables FDA1 and FDA2 of Attachment 1. Ranitidine serum concentrations of subject #'s 25 and 26 are also provided in Attachment 1. The results are similar to those observed for data from 24 subjects. Additional analytical information is provided in Attachment 2. This includes updated tables for quality control samples, back calculated calibration curve standard concentrations, ranitidine concentrations for all 26 subjects, standard curve parameters, repeat analysis and final concentrations, and summary of analyses codes.

2. states that future ranitidine studies will employ a higher LOQ. However, the Cmax values in the current study were greater than 400 times the LOQ and this interference should not effect the results of the bioequivalence comparison (refer to Table FDA2, Attachment 1).

3. Two tables, Tables T5.1 and T6.1, summarize the repeat analyses for this study (Attachment 2). Table T5.1 "The Repeat Analyses and Final Concentrations for Ranitidine in Human Serum" contains all values (originally coded as suspected pharmacokinetic outliers) for which a choice between two evaluable values was made.

RECEIVED

FEB 27 1995

GENERIC DRUGS

If a value was selected as a pharmacokinetic outlier and was repeated in duplicate if possible then the first value along with the repeated value is indicated in this table. If there was only one value available, *i.e.* the original value, this value would not appear in Table T5.1 and the final value would be reported as "NR" in Table T3.1 (Attachment 2). Table T5.1 includes the original value, the reassayed value(s), reason for reassaying, and the rationale for the final value used for the samples:

Table T6.1 "Summary of Analysis Codes for Ranitidine Following a 300 mg Dose" in Attachment 2 lists all repeats from the entire study and the reason for the repeat. The final value for samples listed in this table are also provided in Table T3.1 "Concentrations of Ranitidine in Human Serum Following a 300 mg Dose" (Attachment 2).

Table T5.A (Attachment 3) contains further information on samples that appear in Table T3.1 as "NR" and do not appear in Table T5.1. Table T5.A includes the original value, the reassayed value(s), reason for reassaying and the rationale for the final value use for the samples

4. The waiver request for bioequivalence study requirements for Ranitidine Tablets 150 mg is provided in Attachment 4. A summary of *in-vitro* dissolution data for the test and reference products, a copy of the analytical method, and a copy of the executed batch record for Ranitidine Tablets 300 mg, lot # 6493066, used in the bioequivalence study are also provided in Attachment 4.

5. The samples continue to remain in storage at The statement in the analytical report was incorrect and should indicate that the samples will remain in storage until 25May94 at which time the client will be be contacted regarding further retention of stored samples. This procedure is outlined in the provided in Attachment 5.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

bb/skp
Enclosure

noted 11/6/95
pcs

Geneva pharmaceuticals, inc.

2555 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400 • FAX (303) 466-3717

FEDERAL EXPRESS

TELEPHONE AMENDMENT

27Oct95

Director,
Office of Generic Drugs,
Division of Bioequivalence - HFD-650
Centre for Drug Evaluation and Research,
Metro Park North 2,
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP [redacted]

NC

RE: ANDA 74-467 Ranitidine Hydrochloride Tablets USP, 150 mg and 300 mg
Amendment - Bioequivalence Study

Dear Director:

We are submitting an amendment to our unapproved Abbreviated New Drug Application for Ranitidine Hydrochloride Tablets, in accord with Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation between Jason Gross (FDA) and Sue Panesar (Geneva Pharmaceuticals) on October 12, 1995.

The following data is provided in this amendment:

1. The GLM procedures for the statistical reanalysis of all 26 subjects is provided in Attachment 1.

2. A table with a detailed explanation of repeat values, including sample number, original value, repeat value, and reason for repeat is provided in Attachment 2.

This information is provided for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

bb/skp
Enclosure

RECEIVED
OCT 30 1995
GENERIC DRUGS

Geneva pharmaceuticals, inc.

2555 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400 • FAX (303) 466-3717

FEDERAL EXPRESS

MAJOR AMENDMENT

November 11, 1994

NDA GMC AMENDMENT

Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 74-467 Ranitidine Hydrochloride Tablets USP, 150 mg and 300 mg - Form I
Major Amendment-Chemistry, Manufacturing, Controls and Labeling

Dear Director:

We are submitting an amendment to our unapproved Abbreviated New Drug Application for Ranitidine Hydrochloride Tablets USP, 150 mg and 300 mg - Form I in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to your communication dated June 22, 1994. The following is in response to your comments in the order they appeared in your communication.

A. Chemistry Deficiencies

A Ciba Company

Redacted 5

pages of trade

secret and/or

confidential

commercial

information

Chemistry

B. **Labeling Deficiencies**

In regard to item #B your communication: all of your comments regarding the bottle label have been noted.

Geneva will comply with the Poison Prevention Packaging Act regarding child-resistant closures. We commit our first development batch to be placed on stability with child-resistant closures. Updated Master Packaging Specifications are provided in Attachment 10.

The insert has been revised as requested throughout. Additionally, the HOW SUPPLIED SECTION has been revised to incorporate a change in available bottle sizes.

Final printed bottle labels and draft inserts are provided as requested in Attachment 11.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed and stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

BB/jfo

Geneva pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400 • FAX (303) 466-3717

FEDERAL EXPRESS

November 22, 1995

NDA ORIG AMENDMENT

FPL

Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2 Room 150
7500 Standish Place
Rockville, Maryland 20855

MINOR AMENDMENT

RE: ANDA 74-467 Ranitidine Tablets, USP, 150 mg and 300 mg
Minor Amendment - Chemistry, Labeling

We are submitting an amendment to our unapproved Abbreviated new Drug Application for Ranitidine Tablets, USP, 150 mg and 300 mg in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to your communication dated October 27, 1995, which stated our response would be characterized as a minor amendment.

Chemistry Deficiency

The description for the 300 mg strength tablet has been revised to reflect "Round, standard cup" tablet. Revised finished product specification sheet is provided in Attachment 1.

Labeling Deficiencies

Reference is made to item #'s 1 thru 6 of your communication regarding insert labeling. The insert labeling has been revised as requested and is provided in Attachment 2.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-address envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

BB/ap

Enclosures as indicated

RECEIVED
NOV 24 1995
GENERIC DRUGS

Geneva pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400

FEDERAL EXPRESS

August 29, 1997

AMENDMENT

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

RE: ANDA 74-467 Ranitidine Hydrochloride Tablets, 150 mg and 300 mg
Amendment - Patent and Exclusivity Information

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to our tentatively approved Abbreviated New Drug Application for ANDA 74-467 Ranitidine Hydrochloride Tablets, 150 mg and 300 mg in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96 (a).

Reference is made to calls between Beth Brannan (Geneva) and Peter Rickman (FDA) on 8/28/97.

Per the reference, please find the attached Exclusivity Statement for Ranitidine Hydrochloride Tablets, 150 mg and 300 mg.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

Enclosures

BB/slc

RECEIVED
SEP 2 - 1997
GENERIC DRUGS

GP097

Geneva pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400

FEDERAL EXPRESS

August 28, 1997

Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

RE: ANDA 74-467 Ranitidine Hydrochloride Tablets USP, 150 mg & 300 mg (Form I)
Amendment - Patent Information Summary

Dear Sir:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to our tentatively approved Abbreviated New Drug Application for Ranitidine Hydrochloride Tablets USP, 150 mg & 300 mg (Form I) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96 to provide the following information:

Per 21 CFR 314.107(b)(3) Geneva has met the requirement to receive approval of the Ranitidine Tablet ANDA. The court has not reduced nor extended the 30 month period. The issue of extending or reducing the 30 month period has never even been raised.

Please incorporate this information into ANDA 74-467.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

BB:nb

AUG 29 1997

GP097

Geneva pharmaceuticals, inc.
2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446
(303) 466-2400

FEDERAL EXPRESS

August 27, 1997

Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
1C

RE: ANDA 74-467 Ranitidine Hydrochloride Tablets USP, 150 mg & 300 mg (Form I)
Amendment - Patent Information Summary

Dear Sir:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to our tentatively approved Abbreviated New Drug Application for Ranitidine Hydrochloride Tablets USP, 150 mg & 300 mg (Form I) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96 to provide the following information:

The certification status of the patents listed in the ***Orange Book*** (current through 17th Edition Supplement 4) for Geneva's Ranitidine Tablets is being provided.

4,880,636 (Expiration 5/13/08) - The '636 patent issued on November 14, 1989, but was not listed in the ***Orange Book*** until the June 1995 supplement. Since the patent was not listed within 30 days of issuance and since Geneva submitted an ANDA which contained the appropriate patent certification on February 16, 1994, prior to the late listing of the '636 patent, Geneva is not required to file a paragraph III or paragraph IV certification {21 CFR 314.97(a)(12)(vi)}.

4,521,431 (Expiration 6/4/02) - A paragraph IV certification was filed in Geneva's original application dated 2/16/94. Notification was sent to Glaxo on March 11, 1994. Glaxo's receipt of notice was dated 3/15/94. Glaxo sued within 45 days (4/28/94) - Civil Action No. 94-1921. Copies of the returned receipt and complaint are provided.

Summary Judgment of non-infringement in Geneva's favor was granted by the court on August 6, 1997. Therefore, it is appropriate to base the 30 months from the date of receipt of the Paragraph IV by the patent holder (September 15, 1996).

4,128,658 (Expiration 7/25/97) - The '658 has expired.

AUG 29 1997

GP™

GP097

Therefore, there are no patent issues preventing the approval of Geneva's Ranitidine application and ANDA approval should be granted upon the conclusion of Genpharm's exclusivity (8/29/97).

Please incorporate this information into ANDA 74-467.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan

Beth Brannan, Director
Drug Regulatory Affairs

BB:nb

Enclosure(s)

Geneva pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400 • FAX (303) 438-4600

FEDERAL EXPRESS

AMENDMENT

MINOR AMENDMENT

April 24, 1997

Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 74-467 Ranitidine Hydrochloride Tablets USP, 150 mg and 300 mg (Form I) Minor Amendment - Chemistry and Manufacturing Controls, Labeling: Request for Full Approval at Patent Expiration and Updates to ANDA

Dear Director:

We are hereby submitting a minor amendment to our tentatively approved Abbreviated New Drug Application for Ranitidine Hydrochloride Tablets USP, 150 mg and 300 mg (Form I) in accordance with Section 505(j) of the Food, Drug and Cosmetic Act and with 21 CFR Part 314.(6(a).

Reference is made to your communications dated January 31, 1996 and April 3, 1997 (Labeling).

1. Per Section 505(j)(4)B)(iii) and your communication dated January 31, 1996, Geneva requests full approval of ANDA 74-467 Ranitidine Hydrochloride Tablets USP, 150 mg and 300 mg (Form I) at the expiration of patent 4,128,658 which expires July 25, 1997.

This request is based upon the 30 month rule allowed for in Section 505(j)(4)(B)(iii). The Certified Return Receipt notifying the patent holder of Geneva's intentions was returned signed March 15, 1994. Based on our paragraph IV certification (certifying that Geneva does not infringe upon Glaxo's patent 4,521,431) and the date the notice was signed (March 15, 1994), we calculate that the 30 month period expired September 14, 1996. Therefore, we request that full approval be granted at the expiration of patent 4,128,658 on July 25, 1997.

2. **UPDATES:**

A. Updates and changes to Specifications and Methods:

RECEIVED

APR 25 1997

CENTER FOR DRUGS

Redacted 3

pages of trade

secret and/or

confidential

commercial

information

Specs And methods

Revised Master Manufacturing Forms for both 150 mg and 300 mg strengths are provided in Attachment 2.

C. Packaging:

At this time, we would like to take this opportunity to introduce an additional packaging size for the 150 mg strength. Geneva is proposing an intermediate 100 count packaging size which will be bracketed by the 60 count and 1000 count package sizes that have been submitted previously in this application with appropriate supportive data.

The newly proposed 100 count package size will be packaged in the same packaging configuration as the proposed 60 count package size. Because this is a bracketed package size no accelerated stability is being provided. However, the 100 count package size will be incorporated into Geneva's Long Term Room Temperature Stability Program. Since this is the same container/closure system (60cc bottle/PCR /HS/33 mm) utilized in the packaging of the 60 count package size, all supportive data has been provided in our previous amendment. A revised Master Packaging Specification is provided in Attachment 3.

3. **Labeling:**

Per your faxed communication dated April 3, 1997, the insert has been revised to be in accordance with the provided Labeling Guidance (revised February, 1997). In addition the the changes necessitated by the Labeling Guidance, information pertaining to additional package sizes (refer to our March 13, 1997 amendment to this application and #2C of this communication) has been added in the How Supplied section.

Final printed, revised inserts along with final printed container labeling (inclusive of all proposed package sizes) are provided in Attachment 4.
This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed envelope.

Sincerely,
Geneva Pharmaceuticals, Inc.

Beth Brannan, Director
Drug Regulatory
BB/ap
Enclosures as indicated

Geneva pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400 • FAX (303) 438-4600

FEDERAL EXPRESS

NEW CORRESPONDENCE

Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, Maryland 20855

March 13, 1997

NDA ORIG AMENDMENT
AA

RE: ANDA 74-467 Ranitidine Hydrochloride Tablets USP, 150 mg and 300 mg (Form I) New Correspondence - Chemistry and Manufacturing Controls: Alternate Package Sizes and Tighter Raw Material Specification (Polymorphism)

Dear Director:

We are hereby submitting New Correspondence to our tentatively approved Abbreviated New Drug Application for Ranitidine Hydrochloride Tablets, 150 mg and 300 mg (Form I) in accordance with Section 505(j) of the Food, Drug and Cosmetic Act and with 21 CFR Part 314.96(a).

1. Geneva we would like to take this opportunity add an additional component and packaging counts to our Master Packaging Specifications for both Ranitidine Tablets USP, 150 mg and 300 mg strengths. The following information represents the proposed additions:

Ranitidine Tablets USP 150 mg	**Ranitidine Tablets USP 300 mg**
* Addition of a 60 Count Package Size with a Plastic Child-Resistant Closure (PCR)	* Addition of a 30 Count Package Size with a Plastic Child-Resistant Closure (PCR)
* Addition of a 500 Count Package Size with a Plastic Screw Closure (PSC)	* Addition of a 250 Count Package Size with a Plastic Screw Closure(PSC)

The following data is also provided as support for the proposed additions:

RECEIVED
MAR 14 1997
GENERIC DRUGS

A Ciba Company

• Revised Master Packaging Specifications including the additional sizes for both 150 and 300 mg strengths are provided in Attachment 1.

• Twelve week Accelerated and Eighteen month Accumulated Room Temperature Stability for the 150 mg strength are provided in Attachment 2.

• Twelve Accelerated and Thirteen Month Accumulated Room Temperature Stability for the 300 mg strength are provided in Attachment 3.

• The below supportive component information for each bottle size is provided in Attachment 4.

Containers

- For each bottle size:
  - Certificate of analysis for USP testing
  - Diagrammatic representation
  - Moisture permeation testing for each container/closure
  - Geneva's packaging components specifications and methods
  - Geneva's analytical results

Closures

- For each closure size:
  - Manufacturer's specifications and diagrammatic representation
  - Geneva's specifications and methods for packaging components
  - Geneva's analytical results

Manufacturing equipment, processes and formula remain unaffected by the proposed package size additions.

Geneva has also revised its raw material methodology to detect smaller quantities of polymorphic Form II Ranitidine that might be present in the drug substance. Previously, method allowed for a Limit of Quantitation of NMT % and the specification for Polymorphism was set as "No Form II Detected.

The newly proposed active raw material specification for the Form II Polymorph has been has been changed to NMT %.

The revised methodology utilizes an area of ratio method of quantitating Form II material. We believe that the proposed methodology with its new Limit of Quantitation and specification of NMT % is a reliable quality control test based on linearity and reproducibility studies conducted at Geneva.

Also, in a previous amendment dated June 8, 1995 Geneva added a Related Compounds test for Finished Product in response to a deficiency comment. At this time we wish to add Related Compound testing for the Raw Material to ensure the Raw Material meets Finished Product criteria.

As an additional compendial update to the active raw material specification for the Identification test method has been updated to USP, Supplement 3. The revised raw material method and Specification Sheet are provided in Attachment 5.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed envelope.

Sincerely,

Geneva Pharmaceuticals, INC.

Beth Brannan, Director
Drug Regulatory

BB/ap
Enclosures as indicated

Geneva pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400 • FAX (303) 466-3717

FEDERAL EXPRESS

TELEPHONE AMENDMENT

Director
Office of Generic Drugs
Centre for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

January 30, 1996

RE: ANDA 74-467 Ranitidine Hydrochloride Tablets USP, 150 mg and 300 mg
Telephone Amendment - Patent Statements

Dear Sir:

Geneva Pharmaceuticals, Inc. is hereby submitting a Telephone Amendment to our unapproved Abbreviated New Drug Application for Ranitidine Hydrochloride Tablets USP, 150 mg and 300 mg in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the telephone conversation between Peter Rickman, Branch Chief of Regulatory Support, (OGD) and Beth Brannan (Geneva Pharmaceuticals) on January 30, 1996.

Per CFR 314.107 (f)(2) the following information and Certification are provided:

NOTIFICATION OF LEGAL ACTION

- ANDA Number: 74-467
- Abbreviated New Drug Name: Ranitidine Hydrochloride Tablets USP, 150 mg and 300 mg
- Established Drug Product Name: Ranitidine Hydrochloride Tablets
- Geneva certifies that it is subject to a lawsuit filed by Glaxo Inc., Glaxo Group Limited, and Allen & Harburys Limited, Civil Action Numbers 94-1921 and 94-4589 (NHP) (Consolidated) in the United States District Court for the District of New Jersey April 28, 1994 for infringement of Patent 4,521,431. This action was filed within the 45 day time clock.

Geneva certifies that the content requirements for notification of the patent owner under CFR 314.95 (b) and (c) were met.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

C. Letue for

Beth Brannan, Director
Drug Regulatory Affairs

Geneva pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400 • FAX (303) 466-3717

noted KES 1/31/96

NEW CORRESP NC

FEDERAL EXPRESS

January 22, 1996

Minor Telephone Amendment

RECEIVED JAN 23 1996 GENE...

Acting Director
Office of Generic Drugs
Centre for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

RE: ANDA 74-467 Ranitidine Hydrochloride Tablets USP, 150 mg, and 300 mg
Amendment - Chemistry

Dear Sir:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for Ranitidine Hydrochloride Tablets USP, 150 mg, and 300 mg in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the telephone conversation between Edwin Ramos (FDA) and Archie Phillips (Geneva Pharmaceuticals) on January 22, 1996.

The following data is provided in this amendment:

24 Month Room Temperature Stability Results, Lot # 6493065 - 150 mg and Lot # 6493066 300 mg.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

Enclosures
BB/slc

ORIGINAL

Geneva pharmaceuticals, inc.

2555 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400 • FAX (303) 466-3717

FEDERAL EXPRESS

AMENDMENT

March 11, 1994

Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 74-467, Ranitidine Tablets USP, 150 mg and 300 mg
Amendment - Patent Information

Dear Sir:

We are submitting an amendment to our unapproved Abbreviated New Drug Application for Ranitidine Tablets USP, 150 mg and 300 mg in accordance with Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

Geneva wishes to inform you that the Notice to the Patent owner and to the NDA Holder, as required by Section 505(j)(2)(B)(i)(I) and (II) of the Act, has been given upon receipt of an Acceptance Notification from the FDA for the above referenced application. A copy of Geneva's communication is provided in Attachment #1.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan

Beth Brannan
Director
Drug Regulatory Affairs

BB:jh

Attachments

RECEIVED
MAR 14 1994
GENERIC DRUGS

A Ciba Company

Geneva pharmaceuticals, inc.

2555 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400 • FAX (303) 466-3717

FEDERAL EXPRESS

AMENDMENT

March 2, 1994

Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, Maryland 20855

NEW CORRESP
NC

RE: ANDA 74-467, Ranitidine Tablets USP, 150 mg and 300 mg

Dear Sir:

We are submitting an amendment to our unapproved Abbreviated New Drug Application for Ranitidine Tablets USP, 150 mg and 300 mg in accordance with Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

Reference is made to your telephone communication on March 2, 1994.

The Field Copy Certification for this application has been corrected to state that Geneva certifies the field copy of this application is a true copy of the technical section described in 21 CFR 314.94(a)(9). The revised certification is provided in Attachment #1. Additionally, we are providing a fourth copy of our draft labeling, as requested, in Attachment #2. We apologize for any inconvenience this may have caused.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan
Director
Drug Regulatory Affairs

BB:jh

Attachments

RECEIVED
MAR 3 1994
GENERIC DRUGS

3-10-94

ORIGINAL

A Ciba Company

Geneva pharmaceuticals, inc.

2555 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400 • FAX (303) 466-3717

FEDERAL EXPRESS

3/2/94
52582 (2)(E)

February 16, 1994

Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

RE: Ranitidine Tablets USP, 150 mg and 300 mg - Form I

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting an Abbreviated New Drug Application for Ranitidine Tablets USP, 150 mg and 300 mg as required by Section 505 of the Federal Food, Drug, and Cosmetic Act.

A comprehensive table of contents is provided which shows the volume and page number of our submission's contents, as required by the regulations part 314.94(a)(1).

The blue archival copy contains the complete application. Additionally, the blue archival copy contains a method validation package. Triplicate copies of raw material and finished product specifications have been placed in a plastic sleeve, located just inside the cover.

The red review copy contains labeling and the technical portion of our application. The orange review copy contains bioequivalence information. A bioequivalence study has been completed comparing Geneva's Ranitidine Tablets USP, 300 mg to Zantac® Tablets 300 mg. A full copy of the study and requests for waiver for the 150 mg strength product are provided.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan

Beth Brannan, Director
Drug Regulatory Affairs

RECEIVED
FEB 17 1994
GENERIC DRUGS

Enclosures
BB/jfo