CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 75000

Trade Name Ranitidine Tablets USP 150mg (base) and 300mg (base)

Generic Name Ranitidine Tablets USP 150mg (base) and 300mg (base)

Sponsor Ranbaxy Pharmaceuticals, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75000

APPROVAL LETTER

ANDA 75-000

JAN 30 1998

Ranbaxy Pharmaceuticals, Inc.
Attention: James L Siebert
4600 Marriott Drive - Suite 100
Raleigh, NC 27612

Dear Sir:

This is in reference to your abbreviated new drug application dated November 7, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ranitidine Tablets USP, 150 mg (base) and 300 mg (base).

Reference is also made to your amendments dated May 6, October 31, November 26 and December 13, 1997.

The listed drug product referenced in your application is subject to a period of patent protection which expires on 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 Eastern District of North Carolina (Glaxo Wellcome, Inc. and Glaxo Group Limited v. Ranbaxy Pharmaceuticals Inc., Civil Action No. 5:96CV1068) You also have notified the Agency, that on October 21, 1997, the District Court hearing the patent case issued a Stipulated Order of Dismissal officially terminating the litigation with Glaxo Wellome Inc. and Glaxo Group Limited.

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(base) and 300 mg(base), to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zantac Tablets, 150 mg(base) and 300 mg(base), 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,

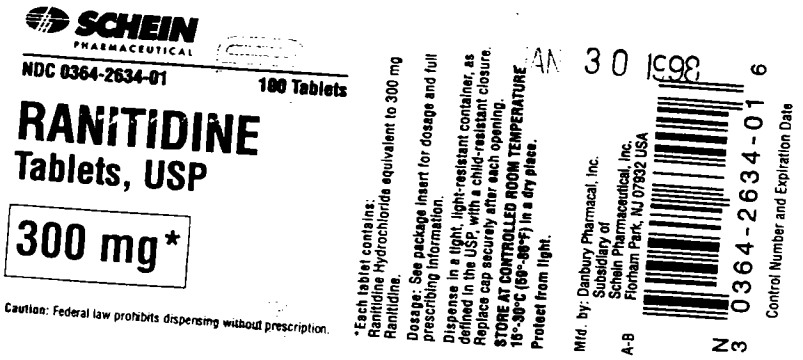
Douglas L. Sporn 1-30-98
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

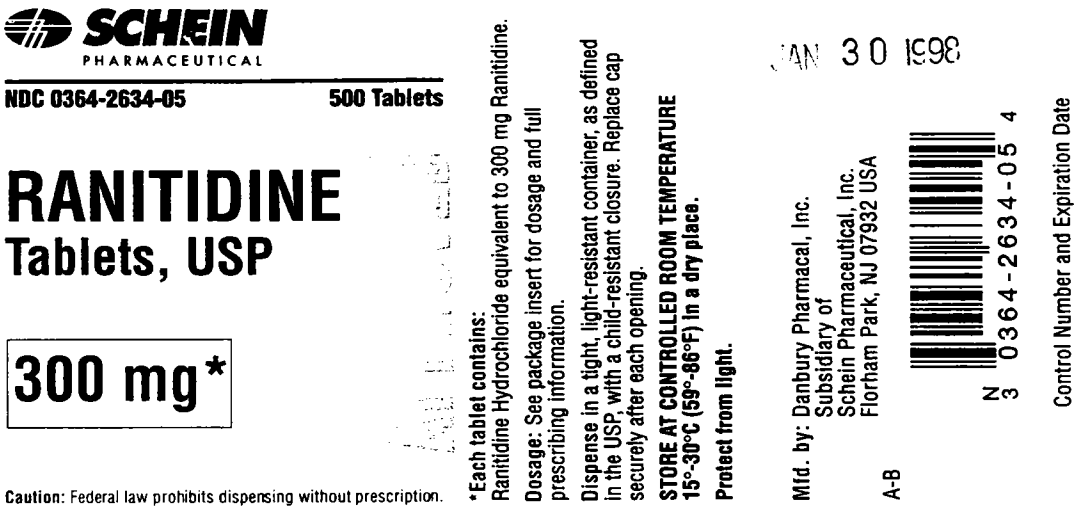
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75000

FINAL PRINTED LABELING


SCHEIN
PHARMACEUTICAL
NDC 0364-2633-01
100 Tablets
RANITIDINE
Tablets, USP
150 mg*
Caution: Federal law prohibits dispensing without prescription
APPROVED
JAN 30 1998
Mfd. by: Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA
A-B
0364-2633-01
Control Number and Expiration Date


SCHEIN
PHARMACEUTICAL
NDC 0364-2634-01
100 Tablets
RANITIDINE
Tablets, USP
300 mg*
Caution: Federal law prohibits dispensing without prescription.
*Each tablet contains:
Ranitidine Hydrochloride equivalent to 300 mg
Ranitidine.
Dosage: See package insert for dosage and full
prescribing information.
Dispense in a tight, light-resistant container, as
defined in the USP, with a child-resistant closure.
Replace cap securely after each opening.
STORE AT CONTROLLED ROOM TEMPERATURE
15°-30°C (59°-86°F) In a dry place.
Protect from light.
JAN 30 1998
Mfd. by: Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA
A-B
N 3 0364-2634-01 6
Control Number and Expiration Date


SCHEIN
PHARMACEUTICAL
NDC 0364-2634-05
500 Tablets
RANITIDINE
Tablets, USP
300 mg*
Caution: Federal law prohibits dispensing without prescription.
*Each tablet contains:
Ranitidine Hydrochloride equivalent to 300 mg Ranitidine.
Dosage: See package insert for dosage and full
prescribing information.
Dispense in a tight, light-resistant container, as defined
in the USP, with a child-resistant closure. Replace cap
securely after each opening.
STORE AT CONTROLLED ROOM TEMPERATURE
15°-30°C (59°-86°F) In a dry place.
Protect from light.
JAN 30 1998
Mfd. by: Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA
A-B
N 3 0364-2634-05 4
Control Number and Expiration Date

SCHEIN
PHARMACEUTICAL

NDC 0364-2633-02 1000 Tablets

RANITIDINE
Tablets, USP

150 mg*

APPROVED

Caution: Federal law prohibits dispensing without prescription.

*Each tablet contains:
Ranitidine Hydrochloride equivalent to 150 mg Ranitidine.

Dosage: See package insert for dosage and full prescribing information.

Dispense in a tight, light-resistant container, as defined in the USP, with a child-resistant closure. Replace cap securely after each opening.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F) In a dry place.

Protect from light.

Mfd. by: Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A-B

30 1998

N 3 0364-2633-02 6

Control Number and Expiration Date

SCHEIN
PHARMACEUTICAL

NDC 0364-2633-05 500 Tablets

RANITIDINE
Tablets, USP

150 mg*

APPROVED

Caution: Federal law prohibits dispensing without prescription.

*Each tablet contains:
Ranitidine Hydrochloride equivalent to 150 mg Ranitidine.

Dosage: See package insert for dosage and full prescribing information.

Dispense in a tight, light-resistant container, as defined in the USP, with a child-resistant closure. Replace cap securely after each opening.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F) In a dry place.

Protect from light.

Mfd. by: Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A-B

30 1998

N 3 0364-2633-05 7

Control Number and Expiration Date

RANITIDINE
Tablets, USP

Revised: November 1997

3631 030

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, HCl. The structural formula is represented below:

$C_{13}H_{22}N_4O_3S$•HCl M.W. 350.87

Ranitidine hydrochloride is a white to pale yellow, crystalline substance that is soluble in water. It has a slightly bitter taste and sulfur-like odor.

Each tablet, for oral administration, contains either 168 mg or 336 mg of ranitidine hydrochloride equivalent to 150 mg or 300 mg ranitidine. In addition, each tablet contains the following inactive ingredients: carnauba wax, castor oil, colloidal silicon dioxide, croscarmellose sodium, ferric oxide yellow, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, talc and titanium dioxide.

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	[illegible]	
Meal	Up to 3	73	79		80
					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 intravenous (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.

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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 per minute, indicating active tubular excretion. Few patients with clinically significant renal function impairment (creatinine clearance 25 to 35 mL per minute) administered 50 mg of ranitidine intravenously had an average plasma half-life of 4.8 hours, a ranitidine clearance of 29 mL per minute, 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 Table I:

Table I

		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%)†		75/169 (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.

Table II

	Mean Daily Doses at Ulcer Healed	
	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.

Double-blind, Multicenter, Placebo-Controlled Trials		Duodenal Ulcer Recurrence
	Drug	0-1 Months
USA	RAN	20%*
	PLC	44%
Foreign	RAN	12%*
	PLC	58%

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

Doses of Antacid	
Ulcer Not Healed	
0.71	
1.43	

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Double-blind, Multicenter, Placebo-Controlled Trials		Duodenal Ulcer Prevalence			
Multicenter Trial	Drug	0-4 Months	0-8 Months	0-12 Months	No. of Patients
USA	RAN	20%*	24%*	35%	138
	PLC	44%	54%	55%	139
Foreign	RAN	12%*	21%*	28%*	174
	PLC	36%	64%	68%	165

% = Life table estimate.
* $p \leq 0.05$ (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 [illegible] 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 on 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.

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.

	Week 4
	Week 8
	Week 12

* All pati
† $p<0.001$

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	Ranitidine*		Placebo*	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
	94	10/83 (12%)	94	10/83 (12%)
		35/69 (51%)†		9/72 (13%)†

g p.r.n. antacids for relief of pain.

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Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome)

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Erosive Esophagitis Patient Healing Rates

	Healed/Evaluable	
	Placebo* n=229	Ranitidine 150 mg b.i.d.* n=215
Week 4	43/198 (22%)	96/206 (47%) †
Week 8	83/178 (36%)	142/200 (71%) †
Week 12	92/159 (58%)	162/192 (84%) †

* All patients were permitted p.r.n. antacids for relief of pain.
† $p \leq 0.001$ 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.

Maintenance of Healing of Erosive Esophagitis: In two multicenter, double-blind, randomized, placebo-controlled, 48-week trials conducted in patients whose erosive esophagitis had been previously healed, ranitidine 150 mg b.i.d. was significantly more effective than placebo in maintaining healing of erosive esophagitis.

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 8 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 mastocytoses).

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 12 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.
7. Maintenance of healing of erosive esophagitis. Placebo-controlled trials have been carried out for 48 weeks.

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.

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 9 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

6

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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 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.

Maintenance of Healing of Erosive Esophagitis: The current recommended adult oral dosage is 150 mg twice 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 per minute 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 150 mg (ranitidine hydrochloride equivalent to 150 mg ranitidine) are unscored, biconvex, round, yellow, film-coated tablets, imprinted on one side "DAN A22" supplied in bottles of 100, 500 and 1000.

Ranitidine Tablets, USP 300 mg (ranitidine hydrochloride equivalent to 300 mg

as the Hydrochloride

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

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.

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Maintenance of Healing of Erosive Esophagitis: The current recommended adult oral dosage is 150 mg twice a day.

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On the bases 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 per minute 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 150 mg (ranitidine hydrochloride equivalent to 150 mg ranitidine) are unscored, biconvex, round, yellow, film-coated tablets imprinted on one side "DAN A22" supplied in bottles of 100, 500 and 1000.

Ranitidine Tablets, USP 300 mg (ranitidine hydrochloride equivalent to 300 mg ranitidine) are unscored, capsule shaped, yellow, film-coated tablets imprinted on one side "DAN A23" supplied in bottles of 100 and 500.

Dispense in a tight, light-resistant container, as defined in the USP, with a child-resistant closure. Replace cap securely after each opening.

Store at controlled room temperature 15°-30°C (59°-86°F), in a dry place.

Protect from light.

Caution: Federal law prohibits dispensing without prescription.

Manufactured by:
Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

Revised: November 1997

7

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75000

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW **NO.2**

2. ANDA **#75-000**

3. NAME AND ADDRESS OF APPLICANT
Ranbaxy Pharmaceuticals Inc.
4600 Marriott Drive - Suite 100
Raleigh, NC 27612

4. LEGAL BASIS FOR ANDA SUBMISSION
The patent for Glaxo Wellcomes Zantac 150, and 300 mg tablets expires on July 25, 1997. Zantac 150 mg and Zantac 300 mg have market exclusivities for the following indications: 1) "maintenance of healing of erosive esophagitis" until November 3, 1997 and 2) "maintenance therapy for gastric ulcer patients at reduced dosage after healing acute ulcers" until March 29, 1998. The company does not intend to include either of these indications in their labeling. To the best of their knowledge, no additional marketing exclusivity is in effect for this product.

5. SUPPLEMENT(S)
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Ranitidine Hydrochloride

9. AMENDMENTS AND OTHER DATES:
Original Application November 7, 1996
FAX Amendment May 6, 1997

10. PHARMACOLOGICAL CATEGORY
H_2 Receptor Antagonist

11. Rx or OTC
Rx

12. RELATED DMFs

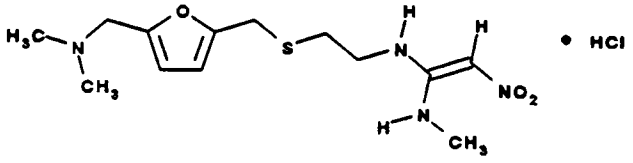
13. DOSAGE FORM
Tablet

14. POTENCY
150 mg and 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.

16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable.

19. REVIEWER — **Tracey Rogers**
DATE COMPLETED — May 19, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75000

BIOEQUIVALENCE REVIEW(S)

MAR 24 1997

Ranitidine HCl Tablets
USP, 150 & 300 mg
ANDA #75-000
Reviewer: Moheb H. Makary
75000SDW.N96

Ranbaxy Pharmaceuticals Inc.
Raleigh, NC.
Submission Date:
November 7, 1996

Review of a Bioequivalence Study, Dissolution Testing and a Waiver Request

I. Objective:

Ranbaxy Pharmaceuticals Inc. has submitted results of a comparative bioequivalence study and dissolution testing conducted on its test product, Ranitidine Hydrochloride Tablets, 300 mg, and Zantac^R Tablets (ranitidine hydrochloride), 300 mg, manufactured by Glaxo Wellcome Inc., as the listed reference product. The firm has requested waiver of in vivo study requirements for its 150 mg strength.

II. Introduction:

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^R 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 Zantac^R. It has been reported in one study that simultaneous administration of Zantac^R with a high potency antacid (150 mmol) reduced the absorption of Zantac^R in fasting subjects. The elimination half-life is reported to be 2.5 to 3 hours (PDR 48, 1994).

III. Protocol #941426 For Single-Dose, Two-Way Crossover Bioavailability Study of Ranitidine 300 mg Tablet Under Fasting Conditions:

Study site:

Sponsor:

Investigators:

Study design:	Single-dose, randomized, 2-way crossover study, under fasting conditions
Subjects:	Thirty-nine (39) healthy adult male

volunteers were selected to participate in this study. Thirty-five (35) subjects successfully completed the study.

Inclusion criteria: The subjects were between 18 and 45 years old. They were within 15% of their ideal weights (Table of "Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983). Each subject received a complete physical examination and laboratory tests of hematopoietic, hepatic and renal functions. Only medically healthy subjects with clinically normal laboratory profiles and negative urine drug and alcohol prior to each phase were enrolled in the study.

Exclusions: Subjects with history or presence of:
-cardiovascular, pulmonary, hepatic, renal, hematological or significant gastrointestinal disease;
-hypersensitivity or idiosyncratic reaction to ranitidine, aspirin or any other histamine H_2-receptor antagonist drugs; diabetes, or complications. were excluded from the study.

Restrictions: The consumption of alcohol beverages, xanthine and caffeine containing foods were prohibited for 24 hours, before dosing and throughout the period of sample collection. Subjects were instructed to take no medication (including OTC) within 7 days prior to start the study.

Dose and treatments: All subjects completed an overnight fast before any of the following drug treatments:

Test product: A. 1X300 mg Ranitidine Tablet (Ranbaxy, Schein), lot # XT6B001, Exp. N/A. lot size [illegible] Tablets, Content uniformity 97.2% (CV=0.9%), potency 98.4%.

Reference product: B. 1x300 mg Zantac® Tablet (Glaxo), lot #5ZPT089, Exp. 5/97, content uniformity 98.5% (CV=1.2%), potency 99.3%.

Food and fluid intake: Single, oral 300 mg (1 Tablet) dose administered with 240 mL of water. Meals were provided at 5 and 10 hours after dosing. Fluids were been allowed one hour before until one hour after dosing.

Blood samples: Blood samples were collected at: 0, 0.33, 0.5, 0.67, 1, 1.33, 1.5, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, and 16. Serum samples were stored frozen at -12°C pending assay.

Washout period: One week

Assay methodology:

Statistical Analysis:

ANOVA was performed at an alpha = 0.05 using the SAS-GLM. The 90% confidence intervals (2 one-sided t-test method) were calculated for LNAUC(0-t), LNAUCinf and LNCmax.

IV. In Vivo Results:

Thirty-nine healthy male volunteers were accepted for entry into the clinical phase of the study. Thirty-five subjects successfully completed both phases of the clinical portion of the study. One volunteer left during check-in. The volunteer who was assigned 37 as a subject number was judged by the study physician to be ineligible for the study due to protocol non-compliance. Subjects #2 and #17 withdrew from the study approximately 1 day prior to their scheduled period 2 dosing due to illness and for personal reasons, respectively. Subjects #22 and #35 fainted 1.5 and 1.8 hours, respectively, prior to period 2 dosing. These events were mild in intensity and were resolved 2 minutes after onset. The medical designated examined the subjects and noted that the subjects became fainted after angiocath insertion.

The serum concentrations and pharmacokinetic parameters are summarized in Table I.

Table I

Mean Serum Concentrations And Pharmacokinetic Parameters
Following An Oral Dose of 300 mg (1x300 mg Tablet)
Ranitidine Under Fasting Conditions
(N=35)

Time (hr)	Ranbaxy Test product Lot #XT6B001 ng/mL (C.V.)	Glaxo Reference product Lot #5ZPT089 ng/mL (C.V.)

0	0.00	0.00
0.33	112.28 (89.2)	71.65 (87.5)
0.50	275.20 (96.0)	195.19 (51.9)
0.67	394.13 (99.7)	313.98 (51.2)
1	506.56 (63.0)	424.57 (38.2)
1.33	639.39 (60.8)	493.38 (50.0)
1.5	713.91 (53.8)	589.33 (85.8)
1.67	697.72 (52.8)	606.53 (59.4)
2	763.67 (51.7)	731.47 (48.7)
2.5	757.75 (37.0)	870.76 (43.6)
3	716.09 (37.0)	900.24 (43.9)
3.5	649.29 (29.9)	783.98 (38.8)
4	599.11 (27.3)	675.01 (31.4)
5	534.95 (29.3)	576.07 (32.5)
6	422.89 (36.5)	442.96 (28.8)
8	251.16 (36.1)	270.39 (36.4)
10	150.98 (45.5)	158.23 (34.0)
12	87.51 (35.4)	96.45 (36.2)
16	33.69 (66.1)	36.68 (55.5)

	Test	Reference	90% CI
AUC(0-t) (ng.hr/mL)	4902.7(19.8)	5168.1(23.3)	
AUCinf (ng.hr/mL)	5100.8(19.0)	5359.0(22.6)	
CMAX (ng/mL)	1037.2(40.7)	1142.7(33.8)	
TMAX (hr)	3.02	2.92	
Kel (1/hr)	0.2433	0.2494	
Half-life (hr)	2.92	2.85	
LNAUC(0-t)			89.5-102.1%
LNAUCinf			90.0-102.2%
LNCMAX			81.7- 97.7%

1. Ranbaxy's test product had an AUC(0-t) of 4902.7 ng.hr/mL and AUCinf of 5100.8 ng.hr/mL, which were 5.1% and 4.8% lower, respectively, than their reference product values. The differences were not statistically significant. The 90% confidence intervals were within the acceptable range of 80-125% for log-transformed AUC(0-t) and AUCinf.

2. The Cmax of Ranbaxy's test product was 1037.2 ng/mL which was 9.2% lower than its reference product value. The difference was statistically significant . The 90% confidence interval of the test mean was within the acceptable range of 80-125% of the reference mean. Some subjects show multiple peaks for both test and reference products.

3. Ranitidine serum levels peaked at 2 and 3 hours for the test and reference products, respectively, following their administration under fasting conditions.

4. It should be noted that the 1.5 hour post-dose blood sample, in period 2 was not obtained from any subject in error. After excluding the 1.5 hour blood sample from the statistical analysis in the study for all subjects, the resulting 90% confidence intervals for ranitidine are as following:

LNAUC(0-t)	89.5-102.2%
LNAUCinf	90.0-102.3%
LNCMAX	81.9- 97.9%

All confidence intervals remain within the acceptable 80-125% range.

V. Formulations:

Ranbaxy's comparative formulations for Ranitidine Tablets 150 mg and 300 mg are shown in Table II.

VI. In Vitro Dissolution Testing:

Method:	USP 23 apparatus II (paddle) at 50 rpm
Medium:	900 mL of deaerated water @ 37°C
Number of Tablets:	12
Test Products:	Ranbaxy's Ranitidine
	150 mg Tablets, lot #XT6B002
	300 mg Tablets, lot #XT6B001
Reference Products:	Glaxo's Zantac®
	150 mg Tablets, lot #5ZPT106
	300 mg Tablets, lot #5ZPT089
Specifications:	NLT in 45 minutes

Dissolution testing results are shown in Table III.

VII. Comments:

1. The confidence intervals for LNAUC(0-t), LNAUCinf and LNCmax are within the acceptable range of 80-125% under fasting conditions.

2. The in vitro dissolution testing for the test products, 150 mg and 300 mg strengths, is acceptable.

3. The formulation for 150 mg strength is proportionally similar to the 300 mg strength of the test product.

VIII. Recommendations:

1. The single-dose bioequivalence study under fasting conditions conducted by Ranbaxy Pharmaceuticals Inc., on its Ranitidine 300 mg Tablets, lot #XT6B001, comparing it to Zantac® 300 mg Tablets manufactured by Glaxo-Wellcome, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Ranbaxy's

Ranitidine Tablet, 300 mg is bioequivalent to the reference product, Zantac^{R} 300 mg Tablets manufactured by Glaxo-Wellcome.

2. The dissolution testing conducted by Ranbaxy Pharmaceuticals Inc., on its Ranitidine 300 mg Tablets, lot #XT6B001, and 150 mg Tablets, lot #XT6B002, comparing them with the respective strengths of Glaxo's Zantac^{R} 300 mg and 150 mg Tablets is acceptable. The formulation for the 150 mg strength is proportionally similar to the 300 mg strength of the test product which underwent acceptable bioequivalence testing. Waiver of in vivo bioequivalence study requirements for the 150 mg tablet of the test product is granted. The Division of Bioequivalence deems Ranitidine Tablet 150 mg, manufactured by Ranbaxy Pharmaceuticals Inc., to be bioequivalent to Zantac^{R} Tablet 150 mg, manufactured by Glaxo-Wellcome.

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 deaerated water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

> 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 above recommendations

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE for RM Date: 3/20/97

Concur: _____ Date: 3/24/97
for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

MMakary/3-20-97 wp 75000SDW.N96
cc: ANDA #75-000, original, HFD-658 (Makary), Drug File, Division File.

Table III. In Vitro Dissolution Testing

Drug (Generic Name):Ranitidine
Dose Strength: 150 mg and 300 mg
ANDA No.: 75-000
Firm: Ranbaxy
Submission Date: November 7, 1996
File Name: 75000SDW.N96

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of water
Specifications: NLT in 45 minutes
Reference Drug: Zantac
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # XT6B002 Strength(mg) 150			Reference Product Lot # 5ZPT106 Strength(mg) 150		
	Mean %	Range	%CV	Mean %	Range	%CV
10	67		7.2	28		15.2
15	78		4.3	42		13.8
20	82		3.9	55		11.9
30	88		3.2	78		8.2
45	92		2.7	92		3.4
60	95		2.3	97		2.2

Sampling Times (Minutes)	Test Product Lot # XT6B001 Strength(mg) 300			Reference Product Lot # 5ZPT089 Strength(mg) 300		
	Mean %	Range	%CV	Mean %	Range	%CV
10	84		9.9	52		13.3
15	89		7.3	72		7.7
20	90		6.0	84		5.4
30	93		4.4	93		2.6
45	96		3.2	97		1.8

60	97		2.5	99		1.6

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75000

CORRESPONDENCE

RANBAXY
PHARMACEUTICALS INC.
4600 MARRIOTT DRIVE-SUITE 100 RALEIGH, NORTH CAROLINA 27612
PHONE: (919) 510 0949 FAX: (919) 510 0958.

May 6, 1997

FACSIMILE
AMENDMENT

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

NEW CORRESP
NC

Reference: Ranitidine Tablets, USP, 150 mg and 300 mg
ANDA 75-000

Dear Sir/Madam:

Reference is made to the above referenced ANDA 75-000.

Reference is also made to the FDA's facsimile deficiency letter dated April 7, 1997. The questions are responded to in the same order as in the letter.

PAGES 2-3 REDACTED

CHEMISTRY

MAY 0 / 1997

A:\RANOGDL.DOC

GENERIC DRUGS

C. LABELING: 12 copies of Final Printed Labeling in Attachment 7

Enclosed please find the following labeling materials which have been revised to be in accordance with the FDA deficiency letter received April 7, 1997:

1. RANITIDINE Tablets, USP 150 mg, 100's, 500's and 1000's final printed, container labels.
2. RANITIDINE Tablets, USP 300 mg, 100's and 500's final printed, container labels.
3. RANITIDINE Tablets, USP final printed, package insert (Revised: April 1997)
4. RANITIDINE Tablets, USP Annotated Side by Side Labeling Comparison.

Also please note that the is being revised with the same specification and test method as in question number 6.

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1) of this submission has been provided to the Food and Drug Administration Atlanta District Office in Atlanta, Georgia.

If you have any questions, please call me at 919-510-0949, ext. 224.

Sincerely,

Jim Sibert /ST

Jim Sibert
Executive Director Regulatory Affairs

RANBAXY
PHARMACEUTICALS INC.
4600 MARRIOTT DRIVE-SUITE 100 RALEIGH, NORTH CAROLINA 27612
PHONE: (919) 510 0949 FAX: (919) 510 0958.

NOV - 7 1996

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

PATENT CERTIFICATION

RE: Ranitidine Tablets USP, 150 mg and 300 mg

Dear Sir/Madam:

The FDA publication entitled "Approved Drug Products With Therapeutic Equivalence Evaluations", 16th Edition (1996) (the "Orange Book") lists U.S. Patent Nos. 4,880,636; 4,521,431; and 4,128,658 in connection with the above-identified drug product.

A. Paragraph III Certification

With respect to U.S. Pat. No. 4,128,658, Ranbaxy Pharmaceuticals Inc. ("RPI"), certifies that in its opinion and to the best of its knowledge, said patent will expire on July 25, 1997.

RPI requests approval of this ANDA effective after July 25, 1997.

B. Paragraph IV Certification

With respect to U.S. Pat. Nos. 4,880,636 and 4,521,431, RPI certifies that in its opinion and to the best of its knowledge, said patents will not be infringed by the manufacture, use, sale, or offer to sell of ranitidine hydrochloride tablets for which this abbreviated new drug application is submitted.

RPI will comply with the requirements under 21 C.F.R. §314.95 (a) with respect to providing a notice to each owner of said patents or their representatives and to the holder of the approved drug application for the listed drug, and with the requirements under 21 C.F.R. §314.95 (c) with respect to the content of the notice.

Sincerely,

Jim Sibert

James L. Sibert
Executive Director, Regulatory Affairs