CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-650

Trade Name:

Generic Name: Famotidine Tablets USP, 20mg and 40mg

Sponsor: Purepac Pharmaceutical Co.

Approval Date: September 14, 2001

Indications: Short term treatment of active duodenal ulcer.

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
Microbiology Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-650

APPROVAL LETTER

ANDA 75-650

SEP 1 4 2001

Purepac Pharmaceutical Co.
Attention: Joan Janulis
200 Elmora Aveune
Elizabeth, NJ 07207

Dear Madam:

This is in reference to your abbreviated new drug application dated June 22, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Famotidine Tablets USP, 20 mg and 40 mg.

Reference is also made to your amendments July 14, and July 29, 1999; and August 20, 2001.

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 Famotidine Tablets USP, 20 mg and 40 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Pepcid® Tablets USP, 20 mg and 40 mg, respectively, of Merck Research Laboratories). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, 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 and 314.98. 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 that 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-40). 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-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 9/14/2001

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-650

MAR 17 2000

Purepac Pharmaceutical Co.
Attention: Joan Janulis
200 Elmora Avenue
Elizabeth, NJ 07207

Dear Madam:

This is in reference to your abbreviated new drug application dated June 22, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Famotidine Tablets USP, 20 mg and 40 mg.

Reference is also made to your amendments dated July 14, and July 29, 1999; and February 9, 2000.

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, (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product), and is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Pepcid Tablets of Merck Research Laboratories, is currently subject to a period of patent protection which expires on October 15, 2000 (U.S. Patent No. 4,283,408 [the '408 patent]). Your application contains a Paragraph III Certification to the '408 patent under Section 505(j)(2)(A)(vii)(III) of the Act stating that you will not market this drug product prior to the expiration of this patent. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until this period has expired, i.e., currently October 15, 2000.

In order to provide for final approval of this application, please submit an amendment at least 60 days (but not more than 90 days) prior to the date you believe your application will be eligible for final approval. This amendment should identify

changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. An amendment should be submitted even if none of these changes were made. This submission should be designated clearly in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.
Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

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

Please note that this drug product 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 product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to October 15, 2000, you should amend your application accordingly.

At the time you submit any amendments, you should contact Kassandra Sherrod, Project Manager, at (301) 827-5849, for further instructions.

Sincerely yours,

Robert Lumpkin for 3/17/00

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-650

APPROVED DRAFT LABELING

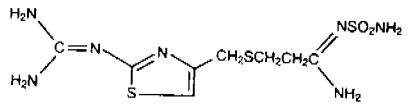
40-8852

FAMOTIDINE TABLETS, USP

Revised — March 2001

DESCRIPTION:

The active ingredient in famotidine is a histamine H_2-receptor antagonist. Famotidine is *N*-(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propanimidamide. The molecular formula of famotidine is $C_8H_{15}N_7O_2S_3$ and its molecular weight is 337.45. Its structural formula is:



Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

Each tablet for oral administration contains either 20 mg or 40 mg of famotidine and the following inactive ingredients: corn starch, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, synthetic red iron oxide, synthetic yellow iron oxide, titanium dioxide, and triacetin. The 40 mg tablet also contains stearic acid.

CLINICAL PHARMACOLOGY IN ADULTS:

GI Effects: Famotidine is a competitive inhibitor of histamine H_2-receptors. The primary clinically important pharmacologic activity of famotidine is inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed by famotidine, while changes in pepsin secretion are proportional to volume output.

In normal volunteers and hypersecretors, famotidine inhibited basal and nocturnal gastric secretion, as well as secretion stimulated by food and pentagastrin. After oral administration, the onset of the antisecretory effect occurred within one hour; the maximum effect was dose-dependent, occurring within one to three hours. Duration of inhibition of secretion by doses of 20 and 40 mg was 10 to 12 hours.

Single evening oral doses of 20 and 40 mg inhibited basal and nocturnal acid secretion in all subjects; mean nocturnal gastric acid secretion was inhibited by 86% and 94%, respectively, for a period of at least 10 hours. The same doses given in the morning suppressed food-stimulated acid secretion in all subjects. The mean suppression was 76% and 84%, respectively, 3 to 5 hours after administration, and 25% and 30%, respectively, 8 to 10 hours after administration. In some subjects who received the 20 mg dose, however, the anti-secretory effect was dissipated within 6-8 hours. There was no cumulative effect with repeated doses. The nocturnal intragastric pH was raised by evening doses of 20 and 40 mg of famotidine to mean values of 5.0 and 6.4, respectively. When famotidine was given after breakfast, the basal daytime interdigestive pH at 3 and 8 hours after 20 or 40 mg of famotidine was raised to about 5.

Famotidine had little or no effect on fasting or postprandial serum gastrin levels. Gastric emptying and exocrine pancreatic function were not affected by famotidine.

Other Effects: Systemic effects of famotidine in the CNS, cardiovascular, respiratory or endocrine systems were not noted in clinical pharmacology studies. Also, no antiandrogenic effects were noted. (See ADVERSE REACTIONS.) Serum hormone levels, including prolactin, cortisol, thyroxine (T_4), and testosterone, were not altered after treatment with famotidine.

Pharmacokinetics: Famotidine is incompletely absorbed. The bioavailability of oral doses is 40-45%. Famotidine Tablets USP, and Famotidine for Oral Suspension are bioequivalent. Bioavailability may be slightly increased by food, or slightly decreased by antacids; however, these effects are of no clinical consequence. Famotidine undergoes minimal first-pass metabolism. After oral doses, peak plasma levels occur in 1-3 hours. Plasma levels after multiple doses are similar to those after single doses. Fifteen to 20% of famotidine in plasma is protein bound. Famotidine has an elimination half-life of 2.5-3.5 hours. Famotidine is eliminated by renal (65-70%) and metabolic (30-35%) routes. Renal clearance is 250-450 mL/min, indicating some tubular excretion. Twenty-five to 30% of an oral dose and 65-70% of an intravenous dose are recovered in the urine as unchanged compound. The only metabolite identified in man is the S-oxide.

There is a close relationship between creatinine clearance values and the elimination half-life of famotidine. In patients with severe renal insufficiency, i.e., creatinine clearance, less than 10 mL/min, the elimination half-life of famotidine may exceed 20 hours and adjustment of dose or dosing intervals in moderate and severe renal insufficiency may be necessary (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).

In elderly patients, there are no clinically significant age-related changes in the pharmacokinetics of famotidine. However, in elderly patients with decreased renal function, the clearance of the drug may be decreased (see PRECAUTIONS, Geriatric Use).

Clinical Studies: Duodenal Ulcer: In a U.S. multicenter, double-blind study in outpatients with endoscopically confirmed duodenal ulcer, orally administered famotidine was compared to placebo. As shown in Table 1, 70% of patients treated with famotidine 40 mg h.s. were healed by week 4.

Table 1
Outpatients with Endoscopically Confirmed Healed Duodenal Ulcers

	Famotidine 40 mg h.s. (N = 89)	Famotidine 20 mg b.i.d. (N = 84)	Placebo h.s. (N = 97)
Week 2	**32%	**38%	17%
Week 4	**70%	**67%	31%

** Statistically significantly different than placebo ($p<0.001$)

Patients not healed by week 4 were continued in the study. By week 8, 83% of patients treated with famotidine had healed versus 45% of patients treated with placebo. The incidence of ulcer healing with famotidine was significantly higher than with placebo at each time point based on proportion of endoscopically confirmed healed ulcers.

In this study, time to relief of daytime and nocturnal pain was significantly shorter for patients receiving famotidine than for patients receiving placebo; patients receiving famotidine also took less antacid than the patients receiving placebo.

Long-Term Maintenance: Treatment of Duodenal Ulcers: Famotidine, 20 mg p.o. h.s. was compared to placebo h.s. as maintenance therapy in two double-blind, multicenter studies of patients with endoscopically confirmed healed duodenal ulcers. In the U.S. study the observed ulcer incidence within 12 months in patients treated with placebo was 2.4 times greater than in the patients treated with famotidine. The 89 patients treated with famotidine had a cumulative observed ulcer incidence of 23.4% compared to an observed ulcer incidence of 56.6% in the 89 patients receiving placebo ($p<0.01$). These results were confirmed in an international study where the cumulative observed ulcer incidence within 12 months in the 307 patients treated with famotidine was 35.7%, compared to an incidence of 75.5% in the 325 patients treated with placebo ($p<0.01$).

Gastric Ulcer: In both a U.S. and an international multicenter, double-blind study in patients with endoscopically confirmed active benign gastric ulcer, orally administered famotidine, 40 mg h.s., was compared to placebo h.s. Antacids were permitted during the studies, but consumption was not significantly different between the famotidine and placebo groups. As shown in Table 2, the incidence of ulcer healing (dropouts counted as unhealed) with famotidine was statistically significantly better than placebo at weeks 6 and 8 in the U.S. study, and at weeks 4, 6 and 8 in the international study, based on the number of ulcers that healed, confirmed by endoscopy.

Table 2
Patients with Endoscopically Confirmed Healed Gastric Ulcers

	U.S. Study		International Study	
	Famotidine 40 mg h.s. (N = 74)	Placebo h.s. (N = 75)	Famotidine 40 mg h.s. (N = 149)	Placebo h.s. (N = 145)
Week 4	45%	39%	†47%	31%
Week 6	†66%	44%	†65%	46%
Week 8	***78%	64%	†80%	54%

***,† Statistically significantly better than placebo ($p\leq0.05$, $p\leq0.01$ respectively)

Time to complete relief of daytime and nighttime pain was statistically significantly shorter for patients receiving famotidine than for patients receiving placebo; however, in neither study was there a statistically significant difference in the proportion of patients whose pain was relieved by the end of the study (week 8).

Gastroesophageal Reflux Disease (GERD): Orally administered famotidine was compared to placebo in a U.S. study that enrolled patients with symptoms of GERD and without endoscopic evidence of erosion or ulceration of the esophagus. Famotidine 20 mg b.i.d. was statistically significantly superior to 40 mg h.s. and to placebo in providing a successful symptomatic outcome, defined as moderate or excellent improvement of symptoms (Table 3).

Table 3
% Successful Symptomatic Outcomes

	Famotidine 20 mg b.i.d (N = 154)	Famotidine 40 mg h.s. (N = 149)	Placebo (N = 73)
Week 6	82††	69	62

††$p\leq0.01$ vs Placebo

By two weeks of treatment symptomatic success was observed in a greater percentage of patients taking famotidine 20 mg b.i.d. compared to placebo ($p\leq0.01$).

Symptomatic improvement and healing of endoscopically verified erosion and ulceration were studied in two additional trials. Healing was defined as complete resolution of all erosions or ulcerations visible with endoscopy. The U.S. study comparing famotidine 40 mg p.o. b.i.d. to placebo and famotidine 20 mg p.o. b.i.d. showed a significantly greater percentage of healing for famotidine 40 mg b.i.d. at weeks 6 and 12 (Table 4).

Table 4
% Endoscopic Healing - U.S. Study

	Famotidine 40 mg b.i.d. (N = 127)	Famotidine 20 mg b.i.d. (N = 125)	Placebo (N = 66)
Week 6	48†††,‡‡	32	18
Week 12	69†††,‡	54†††	29

††† $p\leq0.01$ vs Placebo
‡ $p\leq0.05$ vs famotidine 20 mg b.i.d.
‡‡ $p\leq0.01$ vs famotidine 20 mg b.i.d.

As compared to placebo, patients who received famotidine had faster relief of daytime and nighttime heartburn and a greater percentage of patients experienced complete relief of nighttime heartburn. These differences were statistically significant.

In the international study, when famotidine 40 mg p.o. b.i.d., was compared to ranitidine 150 mg p.o. b.i.d., a statistically significantly greater percentage of healing was observed with famotidine 40 mg b.i.d. at week 12 (Table 5). There was, however, no significant difference among treatments in symptom relief.

Table 5
% Endoscopic Healing - International Study

	Famotidine 40 mg b.i.d. (N = 175)	Famotidine 20 mg b.i.d. (N = 93)	Ranitidine 150 mg b.i.d. (N = 172)
Week 6	48	52	42
Week 12	71‡‡‡	68	60

‡‡‡ $p \leq 0.05$ vs Ranitidine 150 mg b.i.d.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas): In studies of patients with pathological hypersecretory conditions such as Zollinger-Ellison Syndrome with or without multiple endocrine adenomas, famotidine significantly inhibited gastric acid secretion and controlled associated symptoms. Orally administered doses from 20 to 160 mg q 6 h maintained basal acid secretion below 10 mEq/hr; initial doses were titrated to the individual patient need and subsequent adjustments were necessary with time in some patients. Famotidine was well tolerated at these high dose levels for prolonged periods (greater than 12 months) in eight patients, and there were no cases reported of gynecomastia, increased prolactin levels, or impotence which were considered to be due to the drug.

CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS:

Pharmacokinetics: Table 6 presents pharmacokinetic data from published studies of small numbers of pediatric patients given famotidine intravenously. Areas under the curve (AUCs) are normalized to a dose of 0.5 mg/kg I.V. for pediatric patients and compared with an extrapolated 40 mg intravenous dose in adults (extrapolation based on results obtained with a 20 mg I.V. adult dose).

Table 6
Pharmacokinetic Parameters[a] of Intravenous Famotidine

Age (N = number of patients)	Area Under the Curve (AUC) (ng-hr/mL)	Total Clearance (Cl) (L/hr/kg)	Volume of Distribution (V_d) (L/kg)	Elimination Half-life ($T_{1/2}$) (hours)
1-11 yrs (N = 20)	1089 ± 834	0.54 ± 0.34	2.07 ± 1.49	3.38 ± 2.60
11-15 yrs (N = 6)	1140 ± 320	0.48 ± 0.14	1.5 ± 0.4	2.3 ± 0.4
Adults (N = 16)	1726[b]	0.39 ± 0.14	1.3 ± 0.2	2.83 ± 0.99

[a] Values are presented as means ± SD unless indicated otherwise.
[b] Mean value only.

Values of pharmacokinetic parameters for pediatric patients, ages 1-15 years, are comparable to those obtained for adults.

Bioavailability studies of 8 pediatric patients (11-15 years of age) showed a mean oral bioavailability of 0.5 compared to adult values of 0.42 to 0.49. Oral doses of 0.5 mg/kg achieved an AUC of 580 ± 60 ng-hr/mL in pediatric patients 11-15 years of age compared to 482 ± 181 ng-hr/mL in adults treated with 40 mg orally.

Pharmacodynamics: Pharmacodynamics of famotidine were evaluated in 5 pediatric patients 2-13 years of age using the sigmoid E_{max} model. These data suggest that the relationship between serum concentration of famotidine and gastric acid suppression is similar to that observed in one study of adults (Table 7).

Table 7
Pharmacodynamics of famotidine using the sigmoid E_{max} model

	EC_{50} (ng/mL)*
Pediatric Patients	26 ± 13
Data from one study	
a) healthy adult subjects	26.5 ± 10.3
b) adult patients with upper GI bleeding	18.7 ± 10.8

*Serum concentration of famotidine associated with 50% maximum gastric acid reduction. Values are presented as means ± SD.

Four published studies (Table 8) examined the effect of famotidine on gastric pH and duration of acid suppression in pediatric patients. While each study had a different design, acid suppression data over time are summarized as follows:

Table 8

Dosage	Route	Effect[a]	Number of Patients
0.3 mg/kg, single dose	I.V.	gastric pH > 3.5 for 8.7 ± 4.7[b] hours	6
0.4-0.8 mg/kg	I.V.	gastric pH > 4 for 6-9 hours	18
0.5 mg/kg, single dose	I.V.	a > 2 pH unit increase above baseline in gastric pH for > 8 hours	9
0.5 mg/kg b.i.d.	I.V.	gastric pH > 5 for 13.5 ± 1.8[b] hours	4
0.5 mg/kg b.i.d.	oral	gastric pH > 5 for 5.0 ± 1.1[b] hours	4

[a] values reported in published literature.
[b] Means ± SD.

INDICATIONS AND USAGE:

Famotidine Tablets are indicated in:

1. *Short term treatment of active duodenal ulcer.* Most adult patients heal within 4 weeks; there is rarely reason to use famotidine at full dosage for longer than 6 to 8 weeks. Studies have not assessed the

safety of famotidine in uncomplicated active duodenal ulcer for periods of more than eight weeks.

2. *Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer.* Controlled studies in adults have not extended beyond one year.

3. *Short term treatment of active benign gastric ulcer.* Most adult patients heal within 6 weeks. Studies have not assessed the safety or efficacy of famotidine in uncomplicated active benign gastric ulcer for periods of more than 8 weeks.

4. *Short term treatment of gastroesophageal reflux disease (GERD).* Famotidine is indicated for short term treatment of patients with symptoms of GERD (see CLINICAL PHARMACOLOGY IN ADULTS, Clinical Studies).

Famotidine is also indicated for the short term treatment of esophagitis due to GERD including erosive or ulcerative disease diagnosed by endoscopy (see CLINICAL PHARMACOLOGY IN ADULTS, Clinical Studies).

5. *Treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas).* (see CLINICAL PHARMACOLOGY IN ADULTS, Clinical Studies).

CONTRAINDICATIONS:

Hypersensitivity to any component of these products. Cross sensitivity in this class of compounds has been observed. Therefore, famotidine should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

PRECAUTIONS:

General: Symptomatic response to therapy with famotidine does not preclude the presence of gastric malignancy.

Patients with Moderate or Severe Renal Insufficiency: Since CNS adverse effects have been reported in patients with moderate and severe renal insufficiency, longer intervals between doses or lower doses may need to be used in patients with moderate (creatinine clearance <50 mL/min) or severe (creatinine clearance <10 mL/min) renal insufficiency to adjust for the longer elimination half-life of famotidine (see CLINICAL PHARMACOLOGY IN ADULTS and DOSAGE AND ADMINISTRATION).

Drug Interactions: No drug interactions have been identified. Studies with famotidine in man, in animal models, and *in vitro* have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine and antipyrine. Indocyanine green as an index of hepatic drug extraction has been tested and no significant effects have been found.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 106 week study in rats and a 92 week study in mice given oral doses of up to 2000 mg/kg/day (approximately 2500 times the recommended human dose for active duodenal ulcer), there was no evidence of carcinogenic potential for famotidine.

Famotidine was negative in the microbial mutagen test (Ames test) using *Salmonella typhimurium* and *Escherichia coli* with or without rat liver enzyme activation at concentrations up to 10,000 mcg/plate. In *in vivo* studies in mice, with a micronucleus test and a chromosomal aberration test, no evidence of a mutagenic effect was observed.

In studies with rats given oral doses of up to 2000 mg/kg/day or intravenous doses of up to 200 mg/kg/day, fertility and reproductive performance were not affected.

Pregnancy: Pregnancy Category B: Reproductive studies have been performed in rats and rabbits at oral doses of up to 2000 and 500 mg/kg/day, respectively, and in both species at I.V. doses of up to 200 mg/kg/day, and have revealed no significant evidence of impaired fertility or harm to the fetus due to famotidine. While no direct fetotoxic effects have been observed, sporadic abortions occurring only in mothers displaying marked decreased food intake were seen in some rabbits at oral doses of 200 mg/kg/day (250 times the usual human dose) or higher. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Studies performed in lactating rats have shown that famotidine is secreted into breast milk. Transient growth depression was observed in young rats suckling from mothers treated with maternotoxic doses of at least 600 times the usual human dose. Famotidine is detectable in human milk. Because of the potential for serious adverse reactions in nursing infants from famotidine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Patients: Use of famotidine in pediatric patients 1-16 years of age is supported by evidence from adequate and well-controlled studies of famotidine in adults, and by the following studies in pediatric patients: In published studies in small numbers of pediatric patients 1-15 years of age, clearance of famotidine was similar to that seen in adults. In pediatric patients 11-15 years of age, oral doses of 0.5 mg/kg were associated with a mean area under the curve (AUC) similar to that seen in adults treated orally with 40 mg. Similarly, in pediatric patients 1-15 years of age, intravenous doses of 0.5 mg/kg were associated with a mean AUC similar to that seen in adults treated intravenously with 40 mg. Limited published studies also suggest that the relationship between serum concentration and acid suppression is similar in pediatric patients 1-15 years of age as compared with adults. These studies suggest a starting dose for pediatric patients 1-16 years of age as follows:

Peptic Ulcer: 0.5 mg/kg/day p.o. at bedtime or divided b.i.d. up to 40 mg/day.

Gastroesophageal Reflux Disease with or without esophagitis including erosions and ulcerations: 1.0 mg/kg/day p.o. divided b.i.d. up to 40 mg b.i.d.

While published uncontrolled studies suggest effectiveness of famotidine in the treatment of gastroesophageal reflux disease and peptic ulcer, data in pediatric patients are insufficient to establish percent response with dose and duration of therapy. Therefore, treatment duration (initially based on adult duration recommendations) and dose should be individualized based on clinical response and/or pH determination (gastric or esophageal) and endoscopy. Published uncontrolled clinical studies in pediatric patients have employed doses up to 1 mg/kg/day for peptic ulcer and 2 mg/kg/day for GERD with or without esophagitis including erosions and ulcerations.

No pharmacokinetic or pharmacodynamic data are available on pediatric patients under 1 year of age.

Geriatric Use: Of the 4,966 subjects in clinical studies who were treated with famotidine, 488 subjects (9.8%) were 65 and older, and 68 subjects (1.7%) were greater than 75 years of age. No overall differences in safety and effectiveness were observed between these subjects and younger subjects. However, greater sensitivity of some older individuals cannot be ruled out.

No dosage adjustment is required based on age (see CLINICAL PHARMACOLOGY IN ADULTS, Pharmacokinetics). This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Dosage adjustment in the case of moderate or severe renal impairment is necessary (see PRECAUTIONS, Patients with Moderate or Severe Renal Insufficiency and DOSAGE AND ADMINISTRATION, Dosage Adjustment for Patients with Moderate or Severe Renal Insufficiency).

ADVERSE REACTIONS:

The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2500 patients. In those controlled clinical trials in which Famotidine Tablets were compared to placebo, the incidence of adverse experiences in the group which received Famotidine Tablets, 40 mg at bedtime, was similar to that in the placebo group.

The following adverse reactions have been reported to occur in more than 1% of patients on therapy with famotidine in controlled clinical trials, and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%) and diarrhea (1.7%).

The following other adverse reactions have been reported infrequently in clinical trials or since the drug was marketed. The relationship to therapy with famotidine has been unclear in many cases. Within each category the adverse reactions are listed in order of decreasing severity:

Body as a Whole: fever, asthenia, fatigue

Cardiovascular: arrhythmia, AV block, palpitation

Gastrointestinal: cholestatic jaundice, liver enzyme abnormalities, vomiting, nausea, abdominal discomfort, anorexia, dry mouth

Hematologic: rare cases of agranulocytosis, pancytopenia, leukopenia, thrombocytopenia

Hypersensitivity: anaphylaxis, angioedema, orbital or facial edema, urticaria, rash, conjunctival injection

Musculoskeletal: musculoskeletal pain including muscle cramps, arthralgia

Nervous System/Psychiatric: grand mal seizure; psychic disturbances, which were reversible in cases for which follow-up was obtained, including hallucinations, confusion, agitation, depression, anxiety, decreased libido; paresthesia; insomnia; somnolence

Respiratory: bronchospasm

Skin: toxic epidermal necrolysis (very rare), alopecia, acne, pruritus, dry skin, flushing

Special Senses: tinnitus, taste disorder

Other: rare cases of impotence and rare cases of gynecomastia have been reported; however, in controlled clinical trials, the incidences were not greater than those seen with placebo.

The adverse reactions reported for Famotidine Tablets may also occur with Famotidine for Oral Suspension.

OVERDOSAGE:

There is no experience to date with deliberate overdosage. Oral doses of up to 640 mg/day have been given to adult patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

The oral LD_{50} of famotidine in male and female rats and mice was greater than 3000 mg/kg and the minimum lethal acute oral dose in dogs exceeded 2000 mg/kg. Famotidine did not produce overt effects at high oral doses in mice, rats, cats and dogs, but induced significant anorexia and growth depression in rabbits starting with 200 mg/kg/day orally. The intravenous LD_{50} of famotidine for mice and rats ranged from 254-563 mg/kg and the minimum lethal single I.V. dose in dogs was approximately 300 mg/kg. Signs of acute intoxication in I.V. treated dogs were emesis, restlessness, pallor of mucous membranes or redness of mouth and ears, hypotension, tachycardia and collapse.

DOSAGE AND ADMINISTRATION:

Duodenal Ulcer: *Acute Therapy:* The recommended adult oral dosage for active duodenal ulcer is 40 mg once a day at bedtime. Most patients heal within 4 weeks; there is rarely reason to use famotidine at full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective.

Maintenance Therapy: The recommended adult oral dose is 20 mg once a day at bedtime.

Benign Gastric Ulcer: *Acute Therapy:* The recommended adult oral dosage for active benign gastric ulcer is 40 mg once a day at bedtime.

Gastroesophageal Reflux Disease (GERD): The recommended oral dosage for treatment of adult patients with symptoms of GERD is 20 mg b.i.d. for up to 6 weeks. The recommended oral dosage for the treatment of adult patients with esophagitis including erosions and ulcerations and accompanying symptoms due to GERD is 20 mg or 40 mg b.i.d. for up to 12 weeks (see CLINICAL PHARMACOLOGY IN ADULTS, Clinical Studies).

Dosage for Pediatric Patients: See PRECAUTIONS, Pediatric Patients.

The studies described in PRECAUTIONS, Pediatric Patients suggest the following starting doses in pediatric patients 1-16 years of age:

Peptic ulcer: 0.5 mg/kg/day p.o. at bedtime or divided b.i.d. up to 40 mg/day.

Gastroesophageal Reflux Disease with or without esophagitis including erosions and ulcerations: 1.0 mg/kg/day p.o. divided b.i.d. up to 40 mg b.i.d.

While published uncontrolled studies suggest effectiveness of famotidine in the treatment of gastroesophageal reflux disease and peptic ulcer, data in pediatric patients are insufficient to establish percent response with dose and duration of therapy. Therefore, treatment duration (initially based on adult duration recommendations) and dose should be individualized based on clinical response and/or pH determination (gastric or esophageal) and endoscopy. Published uncontrolled clinical studies in pediatric patients have employed doses up to 1 mg/kg/day for peptic ulcer and 2 mg/kg/day for GERD with or without esophagitis including erosions and ulcerations.

No pharmacokinetic or pharmacodynamic data are available on pediatric patients under 1 year of age.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas): The dosage of famotidine in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose for pathological hypersecretory conditions is 20 mg q 6 h. In some patients, a higher starting dose may be required. Doses should be adjusted to individual patient needs and should continue as long as clinically indicated. Doses up to 160 mg q 6 h have been administered to some adult patients with severe Zollinger-Ellison Syndrome.

Oral Suspension: Famotidine for Oral Suspension may be substituted for Famotidine Tablets in any of the above indications.

Concomitant Use of Antacids: Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Moderate or Severe Renal Insufficiency: In adult patients with moderate (creatinine clearance <50 mL/min) or severe (creatinine clearance <10 mL/min) renal insufficiency, the elimination half-life of famotidine is increased. For patients with severe renal insufficiency, it may exceed 20 hours, reaching approximately 24 hours in anuric patients. Since CNS adverse effects have been reported in patients with moderate and severe renal insufficiency, to avoid excess accumulation of the drug in patients with moderate or severe renal insufficiency, the dose of famotidine may be reduced to half the dose or the dosing interval may be prolonged to 36-48 hours as indicated by the patient's clinical response.

Based on the comparison of pharmacokinetic parameters for famotidine in adults and pediatric patients, dosage adjustment in pediatric patients with moderate or severe renal insufficiency should be considered.

HOW SUPPLIED:

Famotidine Tablets are available as follows:

20 mg — Each unscored yellow, round, film coated tablet imprinted with ℞ on one side and 679 on the other contains 20 mg of famotidine USP. Tablets are supplied in bottles of 30 (NDC 0228-2679-03), 90 (NDC 0228-2679-09), and 100 (NDC 0228-2679-11) with a child-resistant closure, 100 (NDC 0228-2679-10), 500 (NDC 0228-2679-50), and 1000 (NDC 0228-2679-96) without a child-resistant closure.

40 mg — Each unscored beige, round, film coated tablet imprinted with ℞ on one side and 641 on the other contains 40 mg of famotidine USP. Tablets are supplied in bottles of 30 (NDC 0228-2641-03), 90 (NDC 0228-2641-09), and 100 (NDC 0228-2641-11) with a child-resistant closure, 100 (NDC 0228-2641-10), 500 (NDC 0228-2641-50), and 1000 (NDC 0228-2641-96) without a child-resistant closure.

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

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

℞ only

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
40-8852

Revised — March 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-650

CHEMISTRY REVIEW(S)

ADDENDUM

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 75-650

3. NAME AND ADDRESS OF APPLICANT
Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, NJ 07207

4. LEGAL BASIS FOR SUBMISSION
The proposed ANDA for Famotidine tablets is the same as the approved, reference listed drug, Pepcid®, the subject of NDA #19-462, held by Merck Research Laboratories (Division of Merck & Co., Inc.)

Patent certification and exclusivity statement are provided (pp. 009-010) U.S Patent No. 4,283,408, Patent Expiration Date: 10/15/00

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
Famotidine Tablets USP

7. NONPROPRIETARY NAME
Famotidine Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: Orig. submission

9. AMENDMENTS AND OTHER DATES:

Firm		FDA	
Orig. submission	6/22/99	Acknowledgement letter	7/16/99
Amendment (phone-bio)	7/29/99	Bio review	8/23/99
		Labeling review	12/6/99
		Deficiency letter	12/7/99
Amendment	2/9/00	Tentatively approved	3/17/00
Amendment	8/15/00	Deficiency FAX	12/19/00
Amendment	1/30/01	Telephone	2/28/01
Amendment (phone)	3/1/01		

This review covers submission dated 1/30 and 3/1/01.

10. PHARMACOLOGICAL CATEGORY
Histamine (H2) Receptor Antagonist

1. Rx or OTC

℞

12. RELATED IND/NDA/DMF(s)

DMF (bulk drug substance)

Other DMFs are identified in the packaging section.

13. DOSAGE FORM

Tablet (Oral)

14. STRENGTH(S)

20 mg and 40 mg

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS N/A

17. COMMENTS

Applicant was informed that has proposed a new acceptance criteria and method of quantitation for the process impurity in the drug substance. Please contact for a revised Certificate of Analysis along with a method for the control of famocyanoamidine. Also submit revise product specification for famocyanoamidine.

18. CONCLUSIONS AND RECOMMENDATIONS

APPROVED

19. REVIEWER: Raymond Brown

DATE COMPLETED: March 2, 2001

Page(s) 4

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Chem. Rev. # 4

3/2/01

DEC 19 2000

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-650 APPLICANT: Purepac Pharmaceutical Company

DRUG PRODUCT: **Famotidine Tablets USP, 20 mg and 40 mg**

The deficiencies presented below represent MINOR deficiencies.

has proposed a new acceptance criteria and method of quantitation for the process impurity in the drug substance. We recommend that you contact ter, then submit a revised Certificate of Analysis along with a method for the control of e. Since you already monitor this impurity in the drug product, please submit a commitment that the drug substance used in the drug product for marketing will meet the new acceptance criteria.

We request that you submit a comparative impurity profile of your drug product and the Reference Listed Drug.

Sincerely yours,

for

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

DEC 7 1999

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75-650 APPLICANT: **Purepac Pharmaceutical Co.**

DRUG PRODUCT: **Famotidine Tablets USP, 20 mg and 40 mg**

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

1. Your COA fails to identify the form. Please identify the correct used in your drug product and provide copies of the test method, chromatograms and data. Also include your specification.

2. We request that you include melting point testing on your COA.

3. You stated that and do not appear in significant quantity in the finished products. Please submit your test methods, established limits and data when tested in the finished product.

4. In your manufacturing instructions it is indicated that the , until the end point of the granulation is reached. Please revise your manufacturing instructions to indicate the exact time for all mixing times.

5. It is indicated that several in-house test methods have been developed for the analysis of the active drug substance and the finished product. Since Famotidine and Famotidine tablets are official monographs in the USP, the approval to use analytical procedures that may differ from that in the USP do not release the firm from any obligation to comply with the methods and procedures in the USP. Therefore, in the event of a dispute, only the results obtained by the official method and procedure in the USP will be considered conclusive.

6. Your controlled room temperature test condition is not complete. You have the option to use the condition of 25° - 30°C at ambient humidity or ICH proposed condition of 25° ± 2°C and 60 ± 5% relative humidity. If your humidity is ambient, please indicate that on the stability sheets.

7. Your release and stability moisture content specifications for both the 20 mg and 40 mg tablets are too high. Please lower your specifications to reflect the data obtained. Revise the appropriate documents and re-submit.

8. We request that you submit controlled room temperature (25°C-30°C) stability data for the full time you have designated the product to be stored in the container closure system. Right now, your designated period is months. You are allowed up to six months with real time stability data. Revise your packaging statement to reflect this change.

9. Drug Master File is currently deficient and the DMF holder has been advised of the deficiencies. A satisfactory resolution of the deficiencies is required by the holder prior to the approval of the application.

Sincerely yours,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-650

BIOEQUIVALENCE

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-650 APPLICANT: Purepac Pharmaceutical Co.

DRUG PRODUCT: Famotidine 20 mg & 40 mg tablets

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

21

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-650 APPLICANT: Purepac Pharmaceutical Co.

DRUG PRODUCT: Famotidine 20 mg & 40 mg tablets

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Famotidine
20 mg & 40 mg tablets
ANDA #75-650
Reviewer: J. Lee
75650SDIW.799

Purepac Pharmaceutical Co.
Elizabeth, New Jersey
Submission date:
June 22, 1999
July 14, 1999
July 29, 1999

Review of Fasted and Fed in-vivo Bioavailability Studies, Dissolution Testing Data and a Request for Waiver

Fasted Study

Study Design:

The clinical study (#P98-335) was conducted at PRACS Institute in Fargo, North Dakota, under the supervision of James D. Carlson, Pharm.D., Principal Investigator.

Thirty-two healthy male volunteers between the ages of 18-45 years and within 15% of ideal body weight for his height and frame were enrolled in the study.

All selected volunteers were in good health as determined by a medical history, physical examination and clinical laboratory tests [hematology, serum chemistry, urinalysis, urine drug screen and HIV test]. All were judged acceptable according to protocol.

The study was designed as a randomized, single-dose, two-way crossover with a 7 day washout period between dosings. Treatments consisted of a single dose of the following:

A. Famotidine
40 mg tablet, batch #PI-0192
Purepac Pharmaceutical Co.
expiry date: Jan, 2001

B. Pepcid®
40 mg tablet, batch #H3527
Merck & Co.
expiry date: October, 2000

Thirty-two subjects were dosed according to the following scheme:

	Period I 02/06/99	Period II 02/13/99
sequence I	A	B
sequence II	B	A

sequence I - subj. # 4, 6, 7, 8, 9, 10, 13, 14, 15, 16, 18, 20, 21, 23, 25, 30

sequence II - subj. #1, 2, 3, 5, 11, 12, 17, 19, 22, 24, 26, 27, 28*, 29, 31, 32

*Subj #28 failed to return for his per II dosing.

After an overnight fast, subjects were given a 40 mg dose of famotidine with 240 ml of water. Fasting continued for ~4 hours post-dose. Blood samples (10 ml) were drawn in Vacutainers containing EDTA at 0 (pre-dose), 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 10, 12, 16 and 24 hours post dose. Samples were collected and cool centrifuged. The harvested plasma samples were then stored frozen at ≤-70°C pending assay. All blood draws were taken as scheduled except for those few listed on page 000987 of the Clinical Report. Deviations were adjusted for in the PK computations.

Of the fifteen adverse events reported only five were considered possibly/probably related to the study drug (headache, faintness). None were considered serious.

There were no deviations from.protocol reported by the subjects.

Analytical: [Not for release under FOI]

Data Analysis:

Plasma data was analyzed by an analysis of variance procedure (SAS 6.12) to determine statistically significant ($p<0.05$) differences between treatments, sequence of dosing, subjects within sequence and periods for the pharmacokinetic parameters. Thirty-one subjects completed the crossover; thirty-one datasets were analyzed.

Results:

No statistically significant differences were found for famotidine in any of the major pharmacokinetic indices on both the original and ln-transformed scales. No sequence effects were observed either. There was a ≤5% difference between the test and reference formulations for plasma levels of famotidine in AUC_{0-t}, AUC_{inf} and C_{max}. The 90% shortest confidence intervals, using least squares means, are presented below:

		90% CI n=31
original scale	AUC_{0-t}	[92.5; 104]
	AUC_{inf}	[92.8; 105]
	C_{max}	[89.1; 103]

	AUC_{0-t}	[92.8; 104]
ln-transformed scale	AUC_{inf}	[93.2; 105]
	C_{max}	[88.6; 103]

Fed Study

Study Design:

The clinical and analytical facilities for this study were the same as that employed in the fasted study. The inclusion and exclusion criteria for subject selection were also the same.

The study (#P98-336) was a randomized, three treatment, three period, six sequence crossover. Treatments consisted of the same two batches of test and reference products (used in the fasted study). A 7 day washout period separated the dosings.

Eighteen subjects were dosed according to the following regimen:

	period I 02/07/99	period II 02/14/99	period III 02/21/99
sequence I	A	B	C
sequence II	A	C	B
sequence III	B	A	C
sequence IV	B	C	A
sequence V	C	A	B
sequence VI	C	B	A

sequence I - subj #6, 12, 17
sequence II - subj #7, 15, 16
sequence III - subj #1, 4, 5
sequence IV - subj #8, 13, 18*
sequence V - subj #9, 10, 14
sequence VI - subj #2, 3, 11

*Subj. #18 was dropped from the study prior to per II dosing due to an ear infection which would have required prescription medication.

Treatment A: 1 x 40 mg famotidine tablet (Purepac) following an overnight fast
Treatment B: 1 x 40 mg famotidine tablet (Purepac) following a standard breakfast*
Treatment C: 1 x 40 mg Pepcid® tablet (Merck) following a standard breakfast*

*standard breakfast: one buttered English muffin
one fried egg
one slice of American cheese
one slice of Canadian bacon
one serving of hash brown potatoes
6 fl oz of orange juice
8 fl oz of whole milk

After an overnight fast, subjects on treatment A were dosed. Those on treatment B or C were served a standard breakfast 30 minutes before dosing. Fasting continued for 4¼ hours post dose. The blood sampling schedule was the same as that used in the fasted study. All blood draws were taken as scheduled except for those listed on page 002633 of the Clinical Report. Those deviations were adjusted for in the PK calculations.

There were four of thirteen adverse events reported that were probably/possibly related to the study drug. These centered around upset stomach, headache, etc. None were considered serious.

Analytical:

The analytical method and validation was the same as that used in the fasted study.

The coefficient of determination (r^2) was ≥0.994 for the standard curves. The coefficient of variation for the standards ranged from 1.78% (at 300 ng/ml; n=18) to 9.3% (at 5.00 ng/ml; n=18)

The precision of the assays was monitored by the quality control samples that were run in triplicate with each group of samples. This data showed:

QC Value	Mean	%CV
7.00 ng/ml (n=41)	7.21	8.6
15.0 ng/ml (n=52)	14.9	8.9
150.0 ng/ml (n=45)	133	5.6
250.0 ng/ml (n=54)	244	6.8

Zero hour samples showed no quantifiable interference at the retention time of the drug peak.

Data Analysis and Results:

Means, standard deviations and CV%s were calculated for AUC_{0-t}, AUC_{inf}, C_{max}, t_{max}, kel, and $t_{½}$ (see attached tables). Areas under the curve and C_{max} showed ≤ 1 % difference for T/R (fed). Absorbance after meals was not affected. Label claim states that the bioavailability of famotidine may be slightly increased by food. A forty minute increase in t_{max} was noted when the drug product was taken with a meal.

In-vitro Dissolution:

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study, using the current USP method. The resultant summaries are attached.

Content Uniformity:

The assay for CU of the Purepac product was 101.6% of label claim (CV=1.4%); for Pepcid®, the CU was 99.2% (CV=0.94%).

Batch Size:

The batch size for the bio-batch of Purepac's 40 mg famotidine tablet was losage units.

Waiver Request:

The sponsor has requested waiver of in-vivo requirements for their 20 mg tablet. A quantitative formulation comparison between the 20 mg & 40 mg tablets were submitted, and comparative dissolution testing results were provided between the company's 20 mg famotidine vs Pepcid® 20 mg tablet.

Recommendation:

1. The bioequivalence studies (fasted & fed) conducted by PRACS Institute for Purepac Pharmaceutical Co. on its famotidine 40 mg tablet, batch #PI-0192, comparing it to Pepcid® 40 mg tablet (Merck) has been found acceptable by the Division of Bioequivalence.

2. The in-vitro dissolution testing (USP) data is also acceptable. 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 0.1M phosphate buffer, pH 4.5 at 37°C using USP XXIII 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 tablet is dissolved in inutes.

3. The Division of Bioequivalence agrees that the information submitted by the sponsor demonstrates that famotidine 20 mg tablet falls under 21 CFR 320.22(d)(2) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted. Purepac's 20 mg famotidine tablet is deemed bioequivalent to Pepcid® 20 mg tablet manufactured by Merck & Co.

4. All bioequivalence criteria have been met.

R. Lee 8/6/99

J. Lee
Division of Bioequivalence

Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

8/10/1999

Concur: /S/ Date: 8/23/99

Dale Conner, Pharm. D.
Director, Division of Bioequivalence

cc:

Drug: Famotidine Tablets, USP
Dose Strengths: 20 mg and 40 mg
Firm: Purepac Pharmaceutical Company
Submission Date: 22-June-1999
File Name: PUR9905

I. Conditions for Dissolution/Release Testing:

Method Ref.:USP 23

USP 23 Apparatus: II	Medium: 0.1 M Phosphate Buffer
RPM: 50	Volume: 900 mL
No. Units Tested: 12	Tolerance (Q):NLT
Reference Drug: PEPCID®	Assay Method:

II. Results of *In Vitro* Dissolution/Release Testing:

Sampling Times (min/hr)	Test Product: Famotidine Lot No.: PI-1092 Strength: **40 mg**			Reference Product: PEPCID® Lot No.: H3527 Strength: **40 mg**		
	Mean %	Range %	% CV	Mean %	Range %	% CV
10	96.16		2.61	94.67		1.18
20	98.6		2.18	97.45		1.17
30	99.31		1.91	97.93		1.09
45	99.93		1.73	98.26		0.91

f_2=87.86

Sampling Times (min/hr)	Test Product: Famotidine Lot No.: PI-1090 Strength: **20 mg**			Reference Product: PEPCID ® Lot No.: H3849 Strength: **20 mg**		
	Mean %	Range %	% CV	Mean %	Range %	% CV
10	100. 8		1.92	101.28		2.18
20	101.62		1.36	101.6		1.65
30	101.69		1.21	101.48		1.83
45	101.71		1.29	101.		0.8

f_2=98.07

Mean Plasma Levels - Fasted
ng/ml (n=31)

Time (HR)	Test Treatment A	(CV%)	Reference Treatment B	(CV%)	Ratio (A/B)
0.00	0.00	.	0.00	.	0.000
0.33	8.39	(136.42)	4.09	(155.01)	2.051
0.67	51.71	(42.47)	43.42	(68.49)	1.191
1.00	83.55	(37.01)	74.42	(46.68)	1.123
1.33	97.47	(34.09)	93.17	(37.53)	1.046
1.67	99.76	(28.98)	102.33	(30.61)	0.975
2.00	103.11	(27.75)	104.00	(26.33)	0.991
2.33	101.71	(27.19)	104.60	(28.03)	0.972
2.67	102.46	(25.51)	105.50	(28.50)	0.971
3.00	98.70	(26.71)	102.63	(28.46)	0.962
3.50	93.08	(28.24)	97.53	(29.20)	0.954
4.00	82.50	(28.20)	88.41	(30.10)	0.933
6.00	52.68	(30.64)	54.16	(36.50)	0.973
8.00	30.39	(29.52)	30.69	(37.91)	0.99
10.00	19.29	(52.59)	18.36	(39.29)	1.051
12.00	10.80	(36.83)	11.06	(41.92)	0.976
16.00	3.09	(117.0)	3.10	(122.41)	0.997
24.00	0.41	(387.10)	0.41	(396.50)	1.000

Pharmacokinetic Parameters - Fasted

Arithmetic

PK Parameter	N	Test Treatment A	(CV%)	N	Reference Treatment B	(CV%)	Ratio (A/B)
AUC	31	644	(27.50)	31	652	(28.43)	0.988
AUCINF	31	680	(27.01)	31	687	(27.78)	0.990
CMAX	31	113.86	(27.36)	31	118.16	(24.84)	0.964
TMAX	31	2.16	(33.21)	31	2.24	(38.45)	0.964
KELM	31	0.2425	(24.68)	31	0.2480	(24.38)	0.978
THALF	31	3.17	(49.25)	31	3.07	(43.60)	1.033
LAUC	31	6.425	(4.80)	31	6.439	(4.61)	0.998
LAUCINF	31	6.483	(4.54)	31	6.492	(4.48)	0.999
LCMAX	31	4.696	(6.21)	31	4.741	(5.40)	0.991

LS Means

PK Parameter	Test Treatment A	Reference Treatment B	Ratio (A/B)	90% CI
AUC	643	653	0.985	-------
LAUC	6.424	6.440	-------	-------
G. Mean	616	626	0.984	(92.8, 104)
AUCINF	679	687	0.988	-------
LAUCINF	6.481	6.493	-------	-------
G. Mean	653	661	0.988	(93.2, 105)
CMAX	113.75	118.26	0.962	-------
LCMAX	4.695	4.742	-------	-------
G. Mean	109.40	114.66	0.954	(88.6, 103)
TMAX	2.17	2.23	0.973	-------
KELM	0.2424	0.2481	0.977	-------
THALF	3.17	3.07	1.036	-------

RMSE

LAUC	0.13604886
LAUCINF	0.1825010
LCMAX	0.02882412

Mean Plasma Levels - Fed
ng/ml (n=17)

Time (HR)	Fasting Test Treatment A	(CV%)	Fed Test Treatment B	(CV%)	Fed Ref Treatment C	(CV%)	Ratio (B/C)	Ratio (B/A)
0.00	0.00	-	0.00	-	0.00	-	-	-
0.33	6.09	(105.47)	4.98	(154.22)	3.17	(146.30)	1.574	0.818
0.67	52.41	(52.63)	24.38	(109.00)	16.99	(131.82)	1.435	0.465
1.00	83.83	(43.66)	40.79	(78.16)	30.35	(96.49)	1.344	0.487
1.33	88.30	(38.63)	59.90	(55.34)	49.70	(60.30)	1.205	0.678
1.67	94.92	(33.72)	70.49	(47.94)	66.51	(44.76)	1.060	0.743
2.00	97.84	(32.41)	80.72	(35.98)	77.44	(33.87)	1.042	0.825
2.33	96.37	(33.19)	83.78	(27.82)	85.48	(26.74)	0.980	0.869
2.67	101.01	(32.08)	90.77	(23.76)	88.78	(25.70)	1.022	0.899
3.00	96.42	(31.71)	89.97	(22.48)	92.64	(27.36)	0.971	0.933
3.50	91.76	(32.44)	88.51	(24.01)	89.14	(23.41)	0.993	0.965
4.00	82.57	(30.01)	84.17	(26.67)	85.29	(22.71)	0.987	1.019
6.00	58.99	(40.98)	55.95	(30.88)	56.75	(27.18)	0.986	0.948
8.00	36.56	(41.39)	33.48	(31.68)	33.07	(30.15)	1.012	0.916
10.00	22.74	(37.06)	21.19	(34.22)	20.97	(35.80)	1.010	0.932
12.00	14.19	(36.10)	13.53	(31.49)	12.75	(44.28)	1.062	0.954
16.00	5.61	(83.37)	4.95	(89.14)	6.11	(61.25)	0.810	0.881
24.00	2.47	(149.97)	0.97	(223.25)	1.25	(233.39)	0.777	0.394

Pharmacokinetic Parameters - Fed

Arithmetic

PK Parameter	N	Test-Fast Treatment A	(CV%)	N	Test-Fed Treatment B	(CV%)	N	Reference Fed Treatment C	CV(%)	Ratio (B/C)	Ratio (B/A)
AUC	17	702	(33.41)	17	611	(21.93)	17	608	(20.46)	1.006	0.871
AUCINF	17	746	(32.34)	17	657	(21.15)	17	649	(19.27)	1.012	0.881
CMAX	17	112.95	(28.22)	17	100.77	(23.52)	17	99.85	(21.40)	1.009	0.892
TMAX	17	2.06	(42.60)	17	2.68	(30.50)	17	2.78	(24.95)	0.962	1.298
KELM	17	0.1980	(31.03)	17	0.1918	(31.91)	17	0.1954	(20.15)	0.981	0.968
THALF	17	3.90	(37.12)	17	4.27	(56.39)	17	3.69	(21.74)	1.155	1.095

LS Means

PK Parameter	N	Test Fast Treatment A	N	Test Fed Treatment B	N	Reference Fed Treatment C	Ratio (B/C)	Ratio (B/A)
AUC	17	702	17	610	17	609	1.002	0.869
LAUC	17	6.492	17	6.389	17	6.392	-----	-----
G. Mean	17	660	17	595	17	597	0.997	0.902
AUCINF	17	747	17	656	17	650	1.009	0.878
LAUCINF	17	6.558	17	6.463	17	6.46	-----	-----
G. Mean	17	705	17	641	17	639	1.003	0.909
CMAX	17	113.47	17	100.85	17	99.82	1.010	0.889
LCMAX	17	4.687	17	4.587	17	4.584	-----	-----
G. Mean	17	108.53	17	98.2	17	97.91	1.003	0.905
TMAX	17	2.03	17	2.68	17	2.79	0.961	1.320
KELM	17	0.1983	17	0.1918	17	0.1957	0.980	0.967
THALF	17	3.91	17	4.26	17	3.68	1.158	1.090

Formulation

Components	Famotidine Tablets USP	
	20 mg	40 mg
1) Famotidine		
2) Microcrystalline Cellulose		
3) Starch		
4) Pregelatinized Starch		
5) Magnesium Stearate		
6) Yellow		
7)		
8)		
TOTAL TABLET WEIGHT		

20 mg tablet: Yellow, round, unscored film-coated tablet imprinted with the Purepac Logo R on one side and 679 on the other side.

40 mg tablet: Beige, round, unscored film-coated tablets, imprinted with Purepac Logo R on one side and 641 on the other side.

Pepcid® products unscored.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-650

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: **75-650** Date of Submission: **June 22, 1999**

Applicant's Name: Purepac Pharmaceutical Co.

Established Name: **Famotidine Tablets USP, 20 mg & 40 mg**

Labeling Deficiencies

1. CONTAINER: (20 mg and 40 mg – 30's, 90's, 100's, 500's and 1,000's)

   Satisfactory in draft.

2. INSERT

   a. GENERAL

      Please note that there are numerous and significant differences between your proposed insert labeling and the referenced listed drug labeling. Please see the attached copy of the Pepcid labeling approved March 18, 1999, and revise accordingly.

   b. DESCRIPTION

      Revise the molecular weight to 337.45 per USP 24.

   c. CLINICAL PHARMACOLOGY IN ADULTS

      i. Pharmacokinetics

         Add "Famotidine Tablets USP, and Famotidine for Oral Suspension are bioequivalent." as the third sentence of the first paragraph.

      ii. Gastric Ulcer

         Add a hyphen between "double" and "blind" in the first sentence of the first paragraph.

   d. PRECAUTIONS (Carcinogenesis, Mutagenesis, Impairment of Fertility)

      Replace "duodena" with "duodenal" in the first paragraph.

   e. ADVERSE REACTIONS

      Add as the last paragraph the following.

      The adverse reactions reported for Famotidine Tablets may also occur with Famotidine for Oral Suspension.

   f. DOSAGE AND ADMINISTRATION

      Add the following subsection after the "Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas)" subsection.

      Oral Suspension: Famotidine for Oral Suspension may be substituted for Famotidine Tablets in any of the above indications.

g. HOW SUPPLIED

We encourage you to relocate "Rx only" to the TITLE section.

Please revise your package insert labeling as instructed above and submit 4 draft copies for a tentative approval or 12 final printed copies of the container labels and insert labeling for a full approval of this application. If draft labels and labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

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 the last submitted labeling with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ATTACHMENT

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?		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	
Do you find the name objectionable? List reasons in FTR, if so, Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			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	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
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	
Labeling(continued)	Yes	No	N.A.
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)			
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. [see FTR]		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ 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

   RLD Info: RLD labeling is Pepcid®; Merck; issued November 1998, Approved March 18, 1999 (NDA 19-462/S-027).

2. INACTIVE INGREDIENTS

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients of components and composition statements on pages 3273 and 3274.

3. PATENTS/EXCLUSIVITIES

   Patent # 4,283,408 EXPIRES October 15, 2000, and there is no protected marketing exclusivity. Firm cites Paragraph III Certification. See page 9.

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   USP: Preserve in well-closed containers, protected from light.
   NDA: Avoid storage at temperatures above 40^0C (104^0F)
   ANDA: Avoid storage of famotidine tablets at temperatures above 40^0C (104^0F)

5. DISPENSING STATEMENT COMPARISON

   USP: Preserve in well-closed containers, protected from light.
   NDA: No recommendation.
   ANDA: Dispense in a tight, light-resistant container as defined in the USP.

6. PACKAGING CONFIGURATIONS

   RLD: 20 mg and 40 mg - Unit-of-use bottles of 30's with CRC, Unit-of-use bottles of 100's with CRC, bottles of 1,000's & 10,000's and unit dose cartons of 100's

   ANDA:20 mg & 40 mg – 30's, 90's, 100's with CRC & 100's, 500's & 1000's with non-CRC.

7. CONTAINER:

8. The descriptions of the tablets in the HOW SUPPLIED section are consistent with that of the application. See pages 4246 and4251.

9. SCORING

   NDA - Not specified
   ANDA - Unscored

10. CLINICAL PHARMACOLOGY (Pharmacokinetics)

    The third sentence comparing tablets and oral solution dosage forms has been modified. it was decided within DLPS that the reference to famotidine oral suspension should be included since it was off patent and to omit the orally disintegrating tablets since it is still protected by patents.

Date of Review: November 23, 1999 **Date of Submission: June 22, 1999**

Primary Reviewer: Koung Lee KL **Date:** 12/3/99

Team Leader: Charlie Hoppes CH **Date:** 12/6/99

DIVISION REVIEW SUMMARY

ANDA 75-650 **DRUG PRODUCT:** Famotidine Tablets USP

FIRM: Purepac Pharmaceutical Co. **DOSAGE FORM:** Tablets (Oral)

STRENGTH(S): 20 mg and 40 mg

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable -
See **ESTABLISHMENT EVALUATION REPORT**, dated 12/22/99.

BIO INFORMATION: Acceptable -
See bio review, dated 8/23/99.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): N/A

STABILITY: Adequate -
Accelerated (40°C/75% RH) stability data are provided for batch nos. PI-1090 and PI-1092, 20 mg and 40 mg tablets respectively. The samples were tested initially, 1, 2 and 3 months in the final marketed container/closure systems (50cc, 200cc and 400cc bottles) The data appear to be adequate and within the specified limits. The stability protocol is adequate and within FDA guidelines. The container/closure systems used in stability studies are the same as those in container section. An expiration dating of 24 month has been granted.

LABELING: Acceptable -
See labeling review, dated / 2/28/00.

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?) Adequate -
Batch #PI1092, s NDS lot #K84029N used.
DMF found **ADEQUATE**, dated 9/99.

SIZE OF STABILITY BATCHES - Adequate -
Batch nos. PI-1090 and PI-1092 have a theoretical yield of tablets. However, the actual yields were tablets and tablets respectively. Batch reconciliation for granulation, and batching yields are provided. Both batches were entired packaged. The batch size meets the Office of Generic Drug's policy #22-90. The batches were manufactured using production scale equipment under production conditions.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?
The proposed maximum production batch size for both strengths is tablets. The manufacturing process is the same as for the exhibit batches.

RECOMMENDATION:
APPROVE

Endorsements:

3/15/2006

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-650

CORRESPONDENCE

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL noted pg 8/27/01

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

ORIG AMENDMENT
N/AM

MINOR AMENDMENT

(CMC Information)

UPS OVERNIGHT COURIER

August 20, 2001

Mr. Gary Buehler, Director
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, MD 20855-2773

RE: ANDA #75-650, Famotidine Tablets USP, 20 mg & 40 mg

Dear Mr. Buehler:

Reference is made to our June 22, 1999 submission of an Abbreviated New Drug Application for Famotidine Tablets USP, 20 mg & 40 mg ANDA #75-650. Further reference is made to your July 31, 2001 letter requesting the submission of a Minor Amendment to the pending application at the time we satisfactorily resolve the cGMP related issues associated with our manufacturing facility.

In accordance with your request, Purepac is providing a statement that representatives of the New Jersey district have determined that our manufacturing facility is in cGMP conformance, based on our most recent inspection.

CENTER FOR DRUG EVALUATION AND RESEARCH RECD AUG 2 1 2001 OGD

In conjunction with this submission, Purepac is providing a copy of this amendment to our local district office. The required Field Copy Certification is included in this amendment.

This concludes our **MINOR AMENDMENT** in response to your letter of July 31, 2001. Purepac Pharmaceutical Co. trusts that you will find this amendment complete and looks forward to the approval of our Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Elizabeth Trowbridge/for

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/bt

JUL 31 2001

ANDA 75-650

Purepac Pharmaceutical Co.
Attention: Joan Janulis
200 Elmora Avenue
Elizabeth, NJ 07207

Dear Madam:

This is in reference to your abbreviated new drug application dated June 22, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Famotidine Tablets USP, 20 mg and 40 mg.

Reference is also made to your amendments dated January 30, March 1, and March 20, 2001.

We have completed the review of this abbreviated application and have concluded that this application is deficient and, therefore, not approvable under 21 CFR 314.125 (b)(13). This is because the Center for Drug Evaluation and Research (CDER) is unable to find that the methods used in, and the facilities and controls used for, the manufacture, processing, packaging or holding of the drug product at Purepac's manufacturing facility at the address stated above comply with current good manufacturing practice (cGMP) regulations.

Our conclusion is based upon a recommendation we received from our Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, to withhold approval of your abbreviated application.

Until such time that you can demonstrate to the Agency that the problems have been corrected and the Agency's concerns are otherwise satisfied, your application cannot be approved.

You should amend this application when the CGMP-related issues have been satisfactorily resolved. Your amendment to the application submitted in response to this not approvable letter will be considered a MINOR AMENDMENT provided that the amendment contains no significant additional information necessary to remedy the cGMP problems. Please include a statement from a

responsible corporate official certifying that your facilities have been found to be in compliance with cGMPs and have been cleared for approval of the drug product by representatives of the local FDA District Office. If, as a result of follow-up inspections related to the ongoing evaluation of this or other applications, it is necessary for you to significantly revise your procedures, controls or practices to correct the deficiencies, then the amendment will be considered to represent a MAJOR AMENDMENT. Your amendment should be plainly marked as such in your cover letter.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120, which will either amend or withdraw this application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 7/31/01

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

cc:

ORIGINAL

A Trusted Name For Over Half A Century

PUREPAC

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

labeling review
drafted 3/27/01
A. Uzzo

LABELING AMENDMENT

UPS OVERNIGHT COURIER

ORIG AMENDMENT

March 20, 2001

N/AF

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Document Control Room
MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-650, Famotidine Tablets, 20 mg and 40 mg

Dear Mr. Buehler:

Reference is made to our June 22, 1999 submission of an Abbreviated New Drug Application for Famotidine Tablets, 20 mg and 40 mg, ANDA #75-650.

Purepac Pharmaceutical Co. is amending the above-referenced application to provide revised package outsert labeling as per the agency's facsimile dated March 15, 2001, containing the innovator's newly approved labeling for Pepcid® Tablets, Oral Suspension and Orally Disintegrating Tablets. In addition to the required revisions, please note that Purepac has revised the insert to be in an outsert format.

Furthermore, as per the agreement between Charlene Salmorin of Purepac and Charlie Hoppes of the Office of Generic Drugs, during the telephone conversation of March 16, 2001, Purepac commits to revise the storage statement on our labels as follows:

"Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F)[see USP Controlled Room Temperature]."

This revision will be instituted at the time of next printing and will be reported in our annual report.

Enclosed please find twelve (12) copies of final printed outsert labeling for your review. Also included in this submission is a side-by-side comparison of our proposed outsert and the listed drug's insert with all differences annotated and explained. If this meets with your approval, please consider this as final printed outsert labeling.

Purepac Pharmaceutical Co. looks forward to your review of this amendment.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Francesca Pisciotta /for

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/fp

Enclosures

A Trusted Name For Over Half A Century
PUREPAC

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

ORIGINAL

TELEPHONE AMENDMENT

(CMC Information)

NDA ORIG AMENDMENT
N/Amn

UPS OVERNIGHT COURIER

March 1, 2001

Mr. Gary Buehler, Acting Director
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, MD 20855-2773

RE: ANDA #75-650, Famotidine Tablets USP, 20 mg and 40 mg

Dear Mr. Buehler:

Reference is made to our June 18, 1999 submission of an Abbreviated New Drug Application for Famotidine Tablets USP, 20 mg & 40 mg, ANDA #75-650. Further reference is made to the February 28, 2001 telephone conversation between Mr. Ray Brown, Chemistry Reviewer at OGD, and Elizabeth Trowbridge, of Purepac, regarding the subject application. In accordance with the agency's request, Purepac is providing revised specification sheets for the finished product and stability testing of the subject products. As requested, these specification sheets have been revised to reflect a limit of "NMT for the process impurity Please note that this revised acceptance criterion is commensurate with the established specification limit for our active drug substance and will apply to the release and stability testing of all commercial batches.

Included in the following table is a comparison of Purepac's revised specification for as included in the respective specification sheets contained in Section 1 of this submission, and our previously submitted specification sheets, contained in our original application:

Testing Stage	Specification			
	Famotidine Tablets USP, 20 mg		Famotidine Tablets USP, 40 mg	
	Original	**Revised**	Original	**Revised**
Finished Product	NMT	**NMT**	NMT	**NMT**
Stability				

In conjunction with this submission, Purepac is providing a copy of this amendment to our local district office. The required Field Copy Certification is included in Section 2.

This concludes our **TELEPHONE AMENDMENT**. Purepac Pharmaceutical Co. trusts that you will find this amendment complete and in order, and looks forward to the approval of our Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2430.

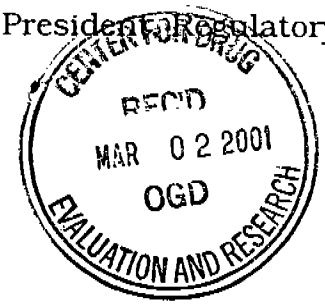
Sincerely,

PUREPAC PHARMACEUTICAL CO.

Elizabeth Trowbridge /for

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/cah
Enclosures



noted 2/2/01 KS

ORIGINAL

A Trusted Name For Over Half A Century

PUREPAC

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

MINOR AMENDMENT

(CMC Information)

UPS OVERNIGHT COURIER

FDA CDER AMENDMENT

January 30, 2001

Mr. Gary Buehler, Acting Director
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, MD 20855-2773

RE: ANDA #75-650, Famotidine Tablets USP, 20 mg and 40 mg

Dear Mr. Buehler:

Reference is made to our June 18, 1999 submission of ANDA #75-650 and to our August 15, 2000 Minor Amendment submitted in accordance with the provisions of our Tentative Approval Letter. Further reference is made to your Minor Chemistry deficiency letter dated December 19, 2000. Your comments are provided in bold type, followed by our firm's response.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 31 2001
OGD

A. CHEMISTRY DEFICIENCIES

Page(s) 1

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Chemistry

In conjunction with this submission, Purepac is providing a copy of this amendment to our local district office. The required Field Copy Certification is included in Section 3.

This concludes our **MINOR AMENDMENT** in response to your letter of December 19, 2000. Purepac Pharmaceutical Co. trusts that you will find this amendment complete and in order, and looks forward to the approval of our Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Elizabeth Trowbridge for

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/cah
Enclosures

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

MINOR AMENDMENT
(CMC Information)

NDA ORIG AMENDMENT
N/A

UPS OVERNIGHT COURIER

August 15, 2000

Mr. Gary Buehler, Acting Director
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 20855-2773

RE: #75-650, Famotidine Tablets USP, 20 mg and 40 mg

Dear Mr. Buehler:

Reference is made to our June 22, 1999 submission of an Abbreviated New Drug Application for Famotidine Tablets USP, 20 mg and 40 mg, ANDA #75-650. Further reference is made to your March 17, 2000 letter stating that this application is tentatively approved. Purepac Pharmaceutical Co. hereby submits this Minor Amendment to the referenced Abbreviated New Drug Application in accordance with the provisions in the tentative approval letter dated March 17, 2000.

Purepac is hereby submitting this Minor Amendment containing updated chemistry, manufacturing and controls (CMC) information. Provided in this amendment is a copy of Purepac's revised method for the particle size determination of the Famotidine drug substance. In addition to format changes, this method was revised to correct a typographical error in the type of filter used in the solution preparation. Please note that this correction accurately reflects the filter employed for the testing performed on the drug substance lot utilized in the manufacture of our test batches. This revised method will be used in the testing of all future lots of Famotidine drug substance. Please refer to Section 1 of this amendment for a copy of the revised method and a listing of the reasons for issue.

MINOR AMENDMENT

ANDA #75-650; Famotidine Tablets USP, 20 mg and 40 mg

In conjunction with this submission, Purepac is providing a copy of this amendment to our local district office. The required Field Copy Certification is included in Section 2 of this submission.

This concludes our **MINOR AMENDMENT** in response to the Agency's request. Purepac Pharmaceutical Co. trusts that you will find this amendment complete and in order, and looks forward to the approval of our Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Elizabeth Tronobridge /for

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/cah
Enclosures

A Trusted Name For Over Half A Century
PUREPAC

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

Mailed Fax 2/18/00

ORIGINAL

ORIG AMENDMENT
N/Am

MINOR AMENDMENT

(CMC, Labeling, and Bioequivalence Information)

UPS OVERNIGHT COURIER

February 9, 2000

Mr. Douglas Sporn, Director
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, MD 20855-2773

RE: ANDA #75-650, Famotidine Tablets USP, 20 mg and 40 mg

Dear Mr. Sporn:

Reference is made to our June 22, 1999 submission of an Abbreviated New Drug Application for Famotidine Tablets USP, 20 mg and 40 mg, ANDA #75-650. Further reference is made to your Minor Chemistry, Labeling and Bioequivalence deficiency letter dated December 7, 1999. Your comments are provided in bold type, followed by our firm's response.

NDA 75-650

A. CHEMISTRY DEFICIENCIES

Page(s) 8

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry

Purepac's Response

On January 5, 2000, Kassandra Sherrod, Project Manager, OGD Division of Chemistry II, verbally confirmed that DMF has no outstanding deficiencies cited, and the DMF is considered satisfactory.

B. LABELING DEFICIENCIES

1. CONTAINER: (20 mg and 40 mg – 30's, 90's, 100's, 500's and 1,000's)

Satisfactory in draft.

2. INSERT (*specific comments are not provided in this letter*)

Please revise your package insert labeling as instructed above and submit 4 draft copies for a tentative approval or 12 final printed copies of the container labels and insert labeling for a full approval of this application. If draft labels and labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

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 the last submitted labeling with all differences annotated and explained.

Purepac's Response

Section 6 of this amendment contains twelve (12) final printed labels for each package size. Please note that Purepac has implemented color-coding for dosage strengths in order to enhance product recognition. This appears as a colored box which includes the product strength and surrounds the product name. Please be advised that no other changes were made and that the label text remains unchanged. Also included are twelve (12) final printed inserts incorporating the requested revisions. In addition, Section 7 contains the side-by-side insert comparisons with all differences annotated and explained.

C. BIOEQUIVALENCE DEFICIENCIES

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Purepac's Response

Purepac acknowledges the comment from the Division of Bioequivalence regarding the above noted dissolution testing specifications. Please be advised that our current finished product and stability specification sheets reflect the referenced dissolution testing conditions and tolerances. These conditions and tolerances are the same as those documented in our original ANDA submission.

In addition, please find enclosed the diskettes (in duplicate) containing the Electronic Submission Documents (ESDs) for the chemistry, manufacturing and controls review part of this amendment, as applicable. Purepac Pharmaceutical Company declares that the data contained in the Electronic Submission Documents are identical to the information contained in the Archival and Review copies of the amendment with the exceptions/explanations provided in Section 8. Please note that EVA version 4.14 as utilized for completing the ESDs in this amendment and that our originally submitted companion document remains unchanged.

In conjunction with this submission, Purepac is providing a copy of this amendment to our local district office. The required Field Copy Certification is included in Section 9.

This concludes our **MINOR AMENDMENT** in response to your letter of December 7, 1999. Purepac Pharmaceutical Co. trusts that you will find this amendment complete and in order, and looks forward to the approval of our Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Elizabeth Trowbridge /for

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/cp
Enclosures: Two (2) Diskettes
CMC EVA ESDs (Original and Duplicate)

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

BIOEQUIVALENCE TELEPHONE AMENDMENT

UPS OVERNIGHT COURIER

July 29, 1999

ORIG AMENDMENT

AB

Douglas Sporn, Director
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 20855-2773

RE: ANDA #75-650, Famotidine Tablets USP, 20 mg and 40 mg

Dear Mr. Sporn:

Reference is made to Purepac's June 22, 1999 submission of an abbreviated new drug application for Famotidine Tablets USP, 20 mg and 40 mg. Further reference is made to the July 22, 1999 telephone conversation between Ms. Jennifer Fan and Ms. Jenny Lee, both from the Division of Bioequivalence, and Elizabeth Trowbridge, of Purepac. During that conversation the following issues were raised:

1. **The raw data (peak heights and peak height ratios for samples, standards, controls, etc.) is missing from the fasting and fed studies. Please provide this data.**

Purepac's Response

Raw data was not provided for all runs in the original ANDA. However, raw data was included for the sample (20% random sampling) contained in the original application. The referenced raw data was included on the following pages:

Study Number	Pages
#P98-335 (Fasting Study)	415 – 420; 594 – 599; 776 – 781; 957 - 962
#P98-336 (Fed Study)	2145 – 2149; 2299 – 2303; 2453 – 2457; 2605 - 2609

Included with this submission are copies of the raw data for all runs for both the fasted and fed studies. Please note that in the data presented the "Sample Name" refers to the Subject-Period-Sample.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUL 30 1999
OGD

2. For the pharmacokinetic calculations, were actual sampling times or nominal times used?

Purepac's Response

In the Summary Section of the Statistical Report the statement *"The following pharmacokinetic parameters were computed from the plasma concentration data using the actual sample collection times"* appears on pages 93 and 1847 for the fasted and fed studies, respectively. The use of the actual sample times for the calculations has been confirmed by PRACS Institute, the contract research organization.

We trust that you will find that the information contained in this Bioequivalence Telephone Amendment addresses the issues raised in the July 22, 1999 conversation and look forward to the review of our Abbreviated New Drug Application.

If you have any questions regarding this submission, please contact the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Elizabeth Trowbridge /for

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

ANDA 75-650

Purepac Pharmaceutical Co.
Attention: Elizabeth Trowbridge
200 Elmora Avenue
New Jersey 07207

JUL 16 1999

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.

NAME OF DRUG: Famotidine Tablets USP, 20 mg and 40 mg

DATE OF APPLICATION: June 22, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 23, 1999

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.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

ELECTRONIC SUBMISSION ESD

July 14, 1999

UPS OVERNIGHT COURIER

75-650

Mr. Douglas Sporn, Director
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 20855-2773

NEW CORRESP
NC
ORIG AMENDMENT
AB

RE: Famotidine Tablets USP, 20 mg and 40 mg

Dear Mr. Sporn,

Reference is made to our June 22, 1999 submission of an Abbreviated New Drug Application, for Famotidine Tablets, USP 20 mg and 40 mg.

In accordance with the Grace Period Announcement that became effective on April 1, 1999, Purepac is hereby submitting the Bioavailability/Bioequivalence and Chemistry, Manufacturing and Controls electronic submission documents (ESDs). The diskettes, submitted in duplicate, contain the information/data files for the BA/BE or CMC review part, as applicable. Therefore, a total of 4 diskettes (1 original and 1 duplicate disk for each review part) are enclosed. Purepac is submitting these electronic Submission Documents within the 30 day grace period permitted from the agency's receipt of our submission.

Purepac Pharmaceutical Company declares that the data contained in the Electronic Submission Document Files is identical to the information contained in the Archival and Review Copies of this application with the following exceptions/explanations:

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUL 15 1999
OGD

General:

- The electronic submission date is June 22, 1999, which is the same date as that of submission of the original paper copy.

CMC Section:

- CMC Packaging System for submission: Since the only difference between the development packaging specification and the final packaging specifications is the deletion of the heading "Development Use Only", the ID numbers of the final packaging specifications are referenced in the electronic submission. Please note that the development packaging specifications were utilized for the exhibit batches and were finalized upon completion of accelerated stability studies.

BA/BE Section:

- EVA, Version 4.13, was used in generating the BA/BE section of this electronic submission. BA/BE Tables, Version April-22-1998, was used to check data entry in associated data tables.
- The electronic submission date noted on the BA/BE section of this ESD is identified as June 22, 1999, the date of the original paper submission.
- Some values generated by the BA/BE Tables program differed from the summary statistics reported in the hard copy of the reports. These differences were negligible and are most likely due to differences in rounding.
- In the Statistics Info section of the EVA submission, a zero was entered for %CV of the least squares means values of each pharmacokinetic parameter. It is understood that %CV may be entered for the arithmetic mean, but it would be inappropriate to associate this with the least squares mean values. "N/A" was entered in these cases.

Purepac Pharmaceutical Co. trusts that you will find this application complete and well organized, and looks forward to the review process. If you have any questions concerning this submission, please do not hesitate to contact the undersigned at telephone number (908) 659-2430, or fax number (908) 659-2440.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/js

Four (4) 3 ½" diskettes enclosed

A Trusted Name For Over Half A Century

PUREPAC

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

June 22, 1999

Mr. Douglas Sporn, Director
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 20855-2773

505(j)(2)(a)
T.M.F

RE: Abbreviated New Drug Application for Famotidine Tablets USP, 20 mg and 40 mg

Dear Mr. Sporn,

In accordance with the regulations promulgated under Section 505(j) of the Federal Food, Drug and Cosmetic Act as amended, Purepac Pharmaceutical Co. is submitting this Abbreviated New Drug Application (Archival and Review Copies) for Famotidine Tablets USP, 20 mg and 40 mg.

This Abbreviated New Drug Application has been prepared in accordance with the current version of the Guidance for Industry entitled "Organization of an ANDA", dated February 1999, and contains a total of twenty (20) volumes, comprising the Archival Copy and the Review Copy (chemistry, manufacturing and controls review part and bioavailability/ bioequivalence review part).

In addition, Electronic Submission Documents (ESDs) for the bioavailability/ bioequivalence (BA/BE) and chemistry, manufacturing and controls (CMC) review parts of this application will be submitted as a correspondence to the ANDA file. The ESDs will be submitted within the 30 day period currently allowed by the Office of Generic Drugs. The required Electronic Submission Document Declaration, stating that the electronic data is identical to the information contained in the Archival and Review copies of the application, will be included with the ESD submission. Please note that the information will be entered via the most current available EVA version.

Furthermore, an electronic version of our proposed package insert, utilizing Microsoft® Word 97 SR-2, accompanies this original ANDA submission (included in the CMC review part). Purepac hereby declares that the text contained in the electronic version of our package insert is identical to the insert text of the hardcopy submission. Please be advised that the electronic insert format differs from that of the hardcopy.

With regard to the packaging of the primary exhibit batches supporting this application, Purepac partially packaged the batches without a previously approved protocol in accordance with Policy and Procedure Guide #41-95 Section E(2). The uniformity data and sampling protocol required by the guidance are contained in Section XII of our application.

In conjunction with this submission, Purepac has provided a Field Copy of this application to our local district office in accordance with 21 CFR 314.94(d)(5). Please note that the required Field Copy Certification is contained in **Section XXI** of our abbreviated application. In addition, The following certifications are provided in this submission:

- A certification in accordance with Section 306(K) of the Federal Food Drug and Cosmetic Act as amended by the "Generic Drug Enforcement Act" **(Section XX)**

- A certification regarding the financial interests and arrangements of the clinical investigators responsible for the treatment or evaluation of research subjects enrolled in the bioequivalence studies supporting this application **(Section VI)**

Three (3) separately bound copies of the analytical methods and related descriptive information are also provided with this original ANDA.

Additionally, Purepac acknowledges that all firms referenced in this ANDA, with respect to the manufacture and testing of the subject drug products, must be in compliance with current good manufacturing practices at the time of approval. A signed acknowledgment is contained in **Section IX** of this application. Purepac also acknowledges that all DMFs referenced in this ANDA have to be found satisfactory at the time of approval of the ANDA.

Purepac Pharmaceutical Co. trusts that you will find this application complete and well organized, and looks forward to the review process. If you have any questions concerning this submission, please do not hesitate to contact the undersigned at telephone number (908) 659-2430, or fax number (908) 659-2440.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Elizabeth Trowbridge /for

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/bt
Enclosures