CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-958

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology And Biopharmaceutics Review

NDA: 20-958	**Name:** Famotidine/Antacid Combination Tablets
Sponsor: Merck & Company, West Point, PA	
Submission Type: Response to Not Approvable Letter	
Submission Date: December 17, 1999, March 10, 2000	
Reviewer: Suresh Doddapaneni, Ph.D.	

What is the nature of the application ?

A Not Approvable letter was sent to the firm for NDA 20-958 on 2/19/99 listing several deficiences. Included in this letter was the following dissolution release test method related comment (see Clinical Pharmacology and Biopharmaceutics review dated 10/20/98 for the original NDA);

"The use of non-whole tablets for dissolution testing is not acceptable to assure accuracy and reproducibility in the method. Revise the dissolution testing method to use whole tablets. We recommend the following revisions: whole tablets [revised] in apparatus II (paddle) at 50 rpm [revised] in 37 ± 0.5°C; and Q= — in 45 minutes. If you accept these recommendations, retest the batches used in the studies and submit the data using the revised method. In addition, submit the method validation data for accuracy and precision for the revised method."

On 10/5/99, the sponsor proposed the use of an alternate method using apparatus III and whole tablets to alleviate the Agency's concerns regarding the ——— step (——— step would negate the ability to detect any significant process or compositional changes to the product through *in vitro* dissolution release test). The Agency agreed in concept to the use of apparatus III (see Clinical Pharmacology and Biopharmaceutics review dated 2/7/00). The Clinical Pharmacology and Biopharmaceutics related data of this submission consists of (I) data supporting the proposed dissolution release test and (II) data demonstrating the *in vivo* bioequivalence famotidine/antacid combination tablets taken with water and without water.

What is the regulatory recommendation?

This submission is acceptable from the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics. The sponsor should be sent the following comment;

"It is recommended that the dissolution specification be set at Q= — in 30 minutes as the data suggests that this is achievable. The approach to bridge the data collected previously and the data to be obtained with the new method as proposed is acceptable to the Agency".

/S/ 4/21/00

Suresh Doddapaneni, Ph.D.
Clinical Pharmacologist, DPE II/OCPB

Shiew-Mei Huang, Ph.D. /S/ 4/21/00

CC:

NDA 20-958, HFD-180 (Division Files), HFD-850 (Lesko), HFD-870 (Doddapaneni, Shiew-Mei Huang), Zom Zadeng (CDR).

4 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

FEB 17 2000

MEMORANDUM

Clinical Pharmacology and Biopharmaceutics Review

NDA: **20-958**

Title: Nonprescription Pepcid —— (Famotidine/antacid combination) chewable tablet

Reviewer: Alfredo R. Sancho, Ph.D. Serial No.: 000

Submission Date: 05 October 1999 Type of Submission: Guidance Request

Dosage: Chewable Tablet (1780 mg total weight) containing 10 mg Famotidine, 800 mg calcium carbonate and 165 mg magnesium hydroxide. The sponsor states that this OTC tablet is for the prevention of heartburn, acid indigestion, and sour stomach.

Sponsor: Merck Research Laboratories.

Address: P. O. Box 4, BLA-20, West Point, PA 19486

SYNOPSIS

The sponsors, in the communicate of 05 October 1999 does not dispute the Agency's recommendation to perform the dissolution testing using the intact drug product in its to-be-marketed formulation. The sponsor does propose to use USP apparatus III, instead of the USP apparatus II, as suggested by the Agency.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmacological Evaluation II has reviewed the information submitted October 05, 1999. The sponsor's proposal of using the whole tablets following the USP apparatus III for the dissolution methods is agreeable.

/S/ 26 Oct 99

Alfredo R. Sancho, Ph.D.
Pharmacology and Biopharmaceutics Reviewer
Radiopharmaceuticals and Medical Imaging Division
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

Note: Team Leader's comment on next page.

2/7/2000.

/S/

/S/

2/7/2000

David J. Lee, Ph.D., Team Leader
Radiopharmaceuticals and Imaging Division
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Cc: HFD-180 NDA 20-958 (1x); DIV.FILE (1x); LEVINE (1X); SANCHO (1X); LEE (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 SHUANG
CDR Attn.: Barbara Murphy

Team Leader's Note:

This TeamLeader concurs with Dr. Sancho's Recommendation. In addition, it should be noted that the use of USP apparatus 3 should be validated and substantiated by additional information. It is acknowledged that the applicant submitted a Response to Not Approval Letter dated 12/17/99. In that submission the Applicant included some data generated using Apparatus 3. As stated above additional information is still needed on usage of Apparatus 3 with the whole-intact-drug product. The reader is referred to the OCPB Review which will be written for 12/17/99 submission.

At this time, No further communication with the applicant is required concerning this submission, ie, dated 10/5/99.

/S/ 2/7/2000

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Clinical Pharmacology and Biopharmaceutics Review

NDA: **20-958**

Title: Nonprescription Pepcid —— (Famotidine/antacid combination) chewable tablet

OCT 20 1998

Reviewer: Alfredo R. Sancho, Ph.D. Serial No.: 000

Submission Date: 23 Feb. 1998 Type of Submission: 1S

Dosage: Chewable Tablet (1780 mg total weight) containing 10 mg Famotidine, 800 mg calcium carbonate and 165 mg magnesium hydroxide. The sponsor states that this OTC tablet is for the prevention of heartburn, acid indigestion, and sour stomach.

Sponsor: Merck Research Laboratories.

Address: P. O. Box 4, BLA-20, West Point, PA 19486

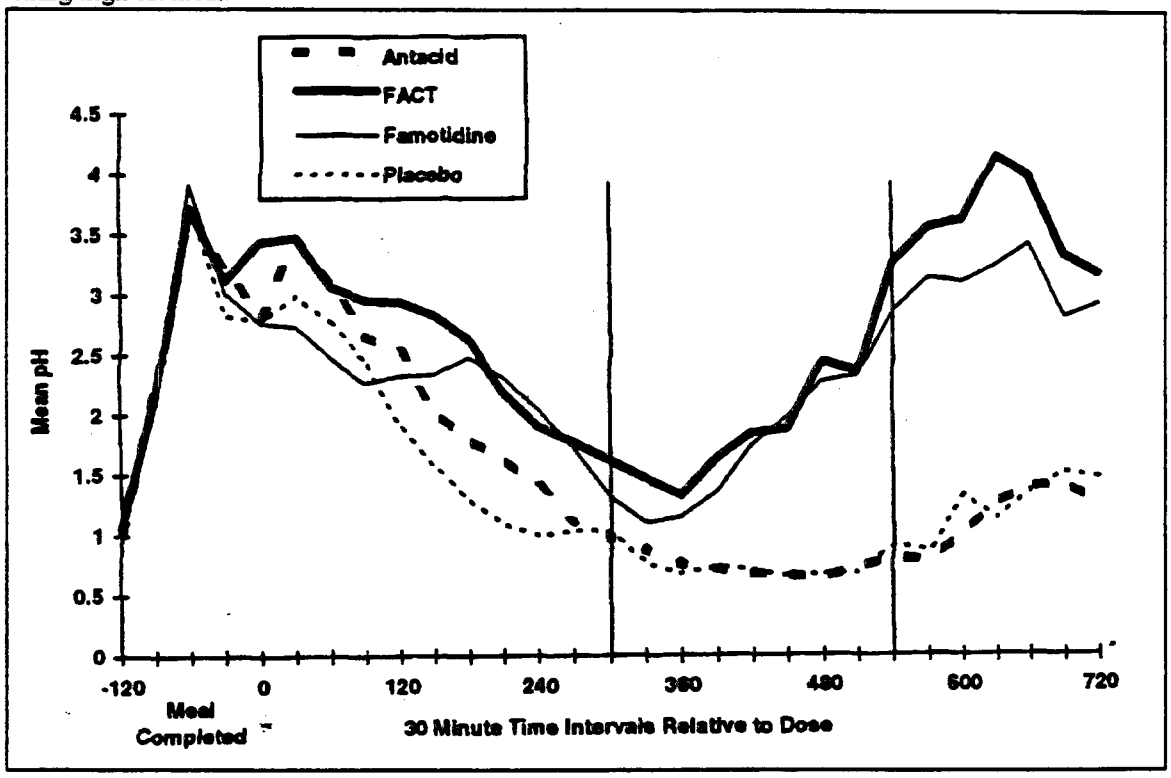
SYNOPSIS

Sponsor states that their drug product "*Pepcid* —— is an OTC compound for the treatment and prevention of heartburn, acid indigestion, and sour stomach. This drug product is referred to in this submission (NDA 20-958) as "Pepcid/Antacid Combination", "Pepcid/Antacid Combination Chewable Tablet", and "Famotidine/Antacid Chewable Tablet", all of which are known as FACT, both in the submission and this review. Other approved Famotidine related products referred to in this submission and review are "PepcidAC Acid Controller Film-Coated Tablets" (FCT) and "PepcidAC Acid Controller Chewable Tablet" (CCT). The sponsor also states on the proposed package insert of this drug product that, "*One tablet should be chewed thoroughly and swallowed with water*" and "*Can be used up to twice daily (up to 2 tablets in 24 hours)*". Furthermore, in the *Warning* section of the same package insert the sponsor states that, "*Do not use with other acid reducers*". The proposed marketable tablet (1780-mg total weight) is chewable and contains *10 mg* Famotidine, *800 mg calcium carbonate*, and *165 mg magnesium hydroxide*. Sponsor states that "The amount of antacid in each tablet provides 21.5 mEq of acid-neutralizing capacity (ANC), which is within the range of doses typically used in OTC antacid products for the treatment of intermittent heartburn." It is also stated in the submission that this product is "a combination product for treating heartburn, which would be faster acting than Famotidine 10-mg alone, while retaining the duration of action associated with Famotidine 10-mg. The data provided in this submission addresses the following areas: 1) the to-be-marketed formulation and dissolution method for Famotidine/Antacid Combination Tablet (FACT); 2) a pharmacokinetic profile comparison (Protocol 095) of FACT compared to Famotidine Film-Coated-Tablets (FCT) during day time in fed state; 3) a pharmacodynamic assessment (Protocol 098) of FACT compared to FCT, an Antacid (ANC), and a Placebo (PBO) during night time in 1-hr after a high fat meal, 4) a bioavailability assessment (Protocol 096) of FACT during the day time in fasted state; and, 5) a pharmacokinetic profile comparison (Protocol 101) of FACT and FCT during the day time in fasted state. The sponsor focused on acid indigestion relief for the first 60 minutes and for the 5 to 9 hour period post-dosing.

RATIONALE FOR PRODUCT

Single dose of antacid alone and Famotidine 10 mg alone relieve heartburn more effectively than placebo. Although both agents are believed to act by reducing the intraluminal acidity their mechanisms of action and pharmacodynamic profiles differ substantially. antacids are believed to work rapidly by neutralizing intraluminal acid on contact. Their duration of action is limited by physiological clearing mechanisms. Famotidine reduces gastric acid production via competitive antagonism of the histamine H_2 receptor. Famotidine 10 mg is believed to require a longer time to onset of pharmacodynamic effect than antacid, but Famotidine has an appreciably longer duration of effect than antacids. These differences suggest that a combination of Famotidine and antacid in 1 chewable tablet would potentially offer the benefits of more rapid relief of symptoms than Famotidine alone, and a longer duration of heartburn relief than antacid alone, as seen in the following chart, an excerpt from the sponsor's submission (page C-10, Figure C-2). In this figure the gastric pH was measured and plotted at one-half hour intervals for each of the treatment regimens from two hours prior to dosing to 12 hours post-dose.

Figure 1. Comparison of intra-gastric mean pH across all four treatments. Dosing was done 1-hr after an evening high fat meal.



TECHNICAL BACKGROUND

The sponsor provided supporting information for the chemistry and manufacturing of the to-be-marketed Pepcid — tablets. The sponsor also provided the batch and stability records for pivotal bioavailability/bioequivalence studies. Throughout the submitted NDA documentation the sponsor interchangeably uses the following terms for the to-be-marketed tablet: *Famotidine/antacid Combination Tablet (FACT)*, *Famotidine-antacid Combination*, Pepcid/antacid combination,

Pepcid/antacid Combination Chewable Tablet, and, Famotidine/antacid chewable tablet. In addition, the Acid Neutralizing Capacity (ANC) was targeted as 21.5 mEq during development and for the to-be-marketed product. Throughout the text of the submission, it is also referred to as 21.5 mEq.

The finished dosage form desired for FACT is a product with good flavor and mouth-feel. Taste masking of Famotidine is necessary in a chewable tablet due to the bitterness of the drug substance. FACT includes the use of coated Famotidine granulation which is the subject of NDA 20-801 for PEPCID® AC Acid Controller Chewable Tablets which was approved by the FDA (*i.e.* referred to as CCT in this submission and review). The other components of FACT and their quantities were selected as the result of studies performed by Johnson & Johnson & Merck Consumer Pharmaceuticals Co. (JJMCP), Fort Washington, PA.

FACT has four major groups of components. These are the ——— Sugar

The individual

and group ingredients are listed in the following table.

Table 1. Description of the ingredients from the proposed to-be-marketed tablet.

Ingredient ***Active ingredient***	**Reference**	**Role**	**mg/tablet**
	DMF		
	USP		
	DMF		
	DMF		
Famotidine			
Famotidine	*USP*		
Lactose Monohydrate	*NF*		
Hydroxypropyl Methylcellulose	*USP*		
	USP		
Cellulose Acetate	*NF*		
Hydroxypropyl Cellulose	*NF*		
	NF		
	NF		
Dextrates	NF		
Sugar			
	NF		
	NF		
Magnesium Stearate	NF		
Rose Colorant Blend			
Red Ferric Oxide	*(NF)*		
	(NF)		
Total Tablet Weight			***1780.00***

(1) Used in the manufacture of tablets, but removed during the manufacturing process.

(2) Contains 98% $Mg(OH)_2$ = 165 mg/tablet.

(3) Contains 95% $CaCO_3$ = 800 mg/ ——— starch NF and a trace quantity of sodium lauryl sulfate NF.

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

DRUG-DRUG INTERACTIONS

No known drug-drug interactions have been identified by the sponsor -using Famotidine (FCT) alone- through human, animal and in-vitro studies. Famotidine, FCT, based on previous studies related to other dosages of Famotidine, does not affect the PK profiles of aminopyrine, antipyrine, diazepam, theophylline, indocyanine green, and phenytoin in humans. It did not potentiate the anticoagulant effect of warfarin in human nor rats, nor did it prolong hexobarbital-induced sleeping in rats. Although not directly studied, concomitant administration of antacids may reduce the absorption of other drugs, such as tetracycline, and iron supplements. No pharmacokinetic/bioavailability studies addressing potential interactions between the active components (*i.e.* antacid and Famotidine) of the proposed chewable tablet were conducted.

FAMOTIDINE PHARMACOKINETICS

Famotidine being an approved drug (NDA 20-235 and 19-462), its pharmacokinetic profile in healthy subjects and the target population is adequately known. From 5 to 40 mg, Famotidine has linear pharmacokinetics and has a "moderately-short" half-life. Following I.V. or P.O. administration, the average $t_{1/2}$ is 2.8 hours in healthy young subjects and 4 hours in healthy elderly subjects. Famotidine is not extensively protein-bound yet shows extensive intersubject variation in plasma and renal clearance. The average plasma and renal clearance averages are 424 ml/min and 316 ml/min, respectively, in healthy young, and 240 ml/min, and 190 ml/min, respectively, in healthy elderly. In renally impaired patients, both parameters are significantly lower. Following oral administration of ^{14}C-Famotidine, an average of 38% of the radioactive dose is recovered in urine and 51% in feces. After IV administration, 71% of the dose is recovered unchanged in the urine. An S-oxide of Famotidine is the only known metabolite. In renally impaired patients. the Famotidine half-life increases disproportionally and may exceed 20 hours in anuric patients.

Following oral administration of PEPCID tablets, average peak plasma levels were 71 ng/ml for the 20-mg tablets and 132 ng/ml for the 40-mg tablets. The time-to-peak for orally administered Famotidine averaged 2.2 hrs and is not, according to the sponsor, dose dependent. In in-vitro studies, Famotidine has low affinity for hepatic microsomal cytochrome P-450 enzyme systems.

Upon oral administration of PEPCID tablet, the average urinary recovery is 28%. The bioavailability of PEPCID tablets average 42% and 45% for the 40-mg and the 20-mg tablets, respectively. The extent of bioavailability is slightly increased in the presence of food and slightly decreased with antacids. However, the sponsor concludes that the effects are small and probably clinically insignificant. The bioavailability of Famotidine from PEPCID tablets is similar for healthy young and healthy elderly subjects. The FACT tablets are bioequivalent to the two other Famotidine preparations used in the initial Merck clinical studies and in Japan.

SUMMARY OF PK, BA, BE, PD AND SELECTED CLINICAL STUDIES.

OBJECTIVES

- To examine the bioequivalence of 10-mg Famotidine/ 21.5-mEq antacid Chewable Tablets (FACT) against 10-mg Famotidine Chewable Tablets (FCT).
- To assess bioavailability of Famotidine from the FACT formulation.
- To evaluate the effect of co-administered antacid (ANC) on the bioavailability of Famotidine.

SUBMITTED STUDY DESIGNS

DOSAGE

The studies included in this submission used randomized, open-label crossover designs with two treatments or more, depending on the study design. Between treatments, the washout periods were of 5 to 7 days. Each subject was randomly placed in different treatment groups. Subjects were also instructed not to consume alcohol nor use tobacco products during the studies.

PROTOCOLS

Three single-dose, two period crossover studies (Protocol 095, 096, and 101) in healthy subjects were performed to characterize the bioavailability of Famotidine 10 mg administered in the proposed formulation. In these studies, 120 ml of water was ingested after the to-be-marketed tablet was chewed and swallowed. The following PK parameters were calculated from the obtained data sets: Mean Plasma Concentration Profile, $AUC_{0\text{-}24hrs.}$ (ng*hr/ml), C_{max} (ng/ml), and T_{max} (hr.). The sponsor's rationale for using $AUC_{0\text{-}24\ hrs}$ as opposed to $AUC_{0\text{-}\infty}$ is that in previously extrapolated $AUC_{0\text{-}\infty}$ the results were found to be small for a dose of 10 mg Famotidine.

An open-label, randomized, four-period, crossover study was also conducted to determine the pharmacodynamic profile of the proposed tablet (Protocol 098). A total of 23 healthy subjects received each of the following four treatments 1 hour after eating a high-fat evening meal: 1) 10 mg Famotidine film-coated-tablet (FCT), 2) the proposed tablet, 3) 1 chewable antacid 21.5 mEq ANC tablet, and, 4) 1 chewable placebo tablet. All treatments were administered with 60 ml of water. An antimony probe was used to measure esophageal and gastric pH from 1 hour before the meal until the next morning, approximately 8 hours.

A Phase IIb study, Protocol 104, was conducted to assess or evaluate the onset and duration of heartburn relief in an at-home scenario. This particular protocol was a double-blind, randomized, single-dose, parallel design, four-site study that randomized 329 frequent heartburn sufferers to 1 of 4 treatment regimens: 1) FACT, the proposed compound, 2) FAM, Famotidine 10 mg, 3) ANC, antacid 21.5 mEq, and, 4) PBO, placebo. Patients ate an evening meal that would regularly cause heartburn. When subjects developed heartburn of a severity they would usually treat, they took the study medication with 60 ml of water. Subjects rated their heartburn and the relief, if any at 10-minute intervals for up to 2 hours post-dose.

Phase III studies were to determine if FACT has a faster onset of symptom control than Famotidine 10 mg FCT, and to determine whether FACT provides a longer duration of relief than antacid 21.5 mEq. Three different heartburn models were employed, yet all three trials were

randomized, double-blind, double-dummy, multi-center, factorial, parallel design with 4 equal-sized treatment groups: 1) FACT, 2) Famotidine 10 mg FCT, 3) antacid 21.5 mEq, and, 4) PBO. The three studies enrolled subjects aged 18 years or older who reported heartburn at least three times per week that was generally relieved with antacids or nonprescription acid reducers. Specifically the studies were: 1) Multiple-Episode Study Protocol 110; 2) Evening Heartburn Study Protocol 109, and, 3) Daytime Heartburn Study Protocol 106.

A Use Study, Protocol 111, was an open-label, in-home use trial that enrolled 496 heartburn sufferers who were randomly recruited at 10 different shopping malls. After signing an informed consent, they received a bottle containing 30 FACT tablets and a draft panel label. Subjects were instructed to read the label and use the product as needed over the following 2 weeks. Each usage occasion was to be recorded in a diary that was to be mailed back to the coordinating site after the 2-week period. A total of 373 subjects returned the diary before the end of the study cutoff date and were included in the data analysis.

Table 2. Summary of subjects/patients included in the studies submitted.

	FACT	Famotidine 10 mg FCT	Antacid 21.5 mEq	Placebo PBO
Subjects				
Single-dose studies	85	86	24	25
Patients				
Single-dose studies	662	667	662	668
Four-dose study	307	311	309	307
Use study (≤30 doses)	465	0	0	0
Total number of individuals	1519	1064	995	1000

SAFETY

Safety was addressed as any clinical adverse experience from all subjects that were enrolled in the nine FACT studies. The same chewable formulation of FACT was used in all nine studies. All adverse experiences were collected through spontaneous patient reporting. The reporting was done in-person for all studies except for the Use Study Protocol 111, in which subjects had to call a central telephone number to report any adverse experiences, since there was no follow-up visit.

PK SAMPLING TIME POINTS

Urine samples were obtained from subjects pre- and post-dosing for urinalysis. Blood samples from each subject were taken for the pre/post-dosing laboratory tests (hematology and biochemistry) and during the studies (at discrete time points) to assay for Famotidine plasma concentrations. Venipuncture using a red top Vacutainer with no anticoagulant was used to collect 7 to 10 ml of whole blood. Samples were allowed to clot by standing at room temperature for 30 to 60 minutes, after which they were centrifuged at ——— for 15 minutes to separate the plasma from other blood components. Samples were kept at —— and assayed for Famotidine levels. Whole blood samples were collected as described in the following tables (minutes and hours separately):

Table 4. Time point distribution for the first 120 minutes in each of the PK studies.

Study	10	20	30	45	60	90	120
095			x		x	x	x
096	x	x	x	x	x	x	x
101			x		x	x	x

Table 5. Time point distribution after the first 120 minutes in each of the PK studies.

Study	2.5	3	4	6	8	10	12	14	24
095	x	x	x	x	x	x	x	x	x
096	x	x	x	x	x	x	x	x	x
101	x	x	x	x	x	x	x	x	x

CLINICAL STUDIES

In the present submission there are 9 (nine) clinical studies conducted for this compound.

Table 3. Summary of studies included in this submission.

Protocol No.	Type	Title
095	Clinical Pharmacology	Open-label, crossover, single-dose study to determine ***bioequivalence*** of FACT and FCT in fed state.
096	Clinical Pharmacology	Open-label, crossover, single-dose study to determine absolute ***bioavailability*** of Famotidine administered in proposed formulation.
098	Clinical Pharmacology	Open-label, crossover, single-dose ***pharmacodynamic*** study measuring esophageal, and gastric pH after administration of FACT components.
101	Clinical Pharmacology	Open-label, crossover, single-dose study to determine ***bioequivalence*** of proposed compound and Famotidine FCT in fasting state.
104	Phase IIb	Double-blind, pilot, factorial, single-dose ***at-home evening*** heartburn study.
106	Phase III	Double-blind, factorial, single-dose ***at-home daytime*** heartburn study to assess ***onset and duration of relief***.
109	Phase III	Double-blind, factorial, single-dose ***in-clinic evening provocative meal*** study to assess ***onset and duration of relief***.
110	Phase III	Double-blind, factorial, ***multiple (4)-episode***, ***at-home*** study to assess ***onset and duration*** of heartburn relief.
111	Use Study	Open-label, uncontrolled, ***multiple-dose***, pattern of use study.

PD SAMPLING TIME POINTS

Intra-esophageal and Intra-gastric pH:

The pH assessments were to be accomplished with antimony, disposable pH catheters. The catheters were used for one treatment period and then discarded. The pH values were collected at [redacted] and stored in a small [redacted] data collection unit [redacted] Esophagram Software 7.0, from Synectics Medical, was utilized to download the data and generate ASCII formatted files for each assessment. The parameters used for the assessment of reflux were: 1) Acid exposure time (percentage of

time pH <4.0); 2) Number of reflux periods, defined as a fall of esophageal pH from pH 5.0 or above to below 4.0 (a new reflux was not considered to have begun unless in the interim the pH had reached 5.0 or above); 3) Mean duration of reflux episodes where pH <4.0.

PK Analytical Methods

Determination of Famotidine in human plasma was done using a [redacted] with ultraviolet (UV) absorbance detection. Absolute bioavailability testing included a solid phase extraction (SPE) and a protein precipitation with [redacted] Both methods had a Limit of Sensitivity of [redacted]

The analytical methods and their limits of quantification or sensibility used to assay biological samples for Famotidine from all three studies included in this NDA submission are summarized in the following table:

Table 6. Analytical methods for Famotidine levels in blood samples.

Study	Biological Fluid	Assay Method	Sensitivity
095	Plasma	[redacted]	
096	Plasma		
101	Plasma		

PD Analytical Methods

Area under the intra-esophageal pH *vs.* time curve measurements 0 to 60 minutes post-dose (onset parameter); and area under the intra-gastric pH *vs.* time curve measured 5 to 9 hours post-dose (duration parameter). The primary treatment comparisons were the FACT *vs.* FCT for onset and FACT *vs.* ANC for duration. The secondary parameter is the area under the intra-gastric pH *vs.* time curve measured 0 to 60 minutes post-dose.

Results

Demographics

Within the subjects included in all four studies, there were several individuals that were reported to be smokers, former smokers, tobacco users, and consumers of alcohol in different degrees. They were instructed to abstain from using alcohol and tobacco substances during the study. The demographic data distribution and dietary pre/post treatment procedures are summarized as follows (means and ranges when appropriate).

Table 7. Demographic analysis of subjects from all four PK/PD studies

Study	Washout time	Fasting Pre-dose	Gender	Age
095	5 –7 days	8 hrs	13F/11M	28.4
096	5 – 7 days	8-hrs	4-F/9-M	29.3
098	3 – 14 days	8-hrs	15-F/12-M	37.4
101	5 – 7 days	8-hrs	5-F/7-M	25.7

DRUG LOTS

A comparison of the reviewed studies and each of their tier groups with dose, dosage form, strength, and lot number for test drug used is summarized in the next table.

Table 8. Manufacturing summary on both drugs used in all four PK/PD studies.

Study	Group	Dose	Dosage Form	Batch size	Lot No.
095	FACT	10-mg	Tablet		C-675-8C
	FCT	10-mg	Tablet		SBH-141
096	FACT	10-mg	Tablet		C-675-8C
	FCT	10-mg	Solution		0529D
098	FACT	10-mg	Tablet		C-675-8C
	FCT	10-mg	Tablet		C-681-1F
	ANC	21-mEq	Tablet		C-659-1A
	PLACEBO	-	Tablet		C-657-1B
101	FACT	10-mg	Tablet		C-675-8C
	FCT	10-mg	Tablet		SDH-222

All four lots of the drug product (C-675-8B, C-675-8C, C-675-8E, C-675-8G) were packaged in [redacted]
Each package contained three of the four lots listed previously. All batches tested meet the proposed specifications when stored at 25°C/66% room humidity, Q= — at 45 minutes.

DISSOLUTION METHOD

The dissolution method for FACT is a modification of that for PEPCID™ 10-mg CCT. FACT contains the same coated —— Famotidine particles as PEPCID™ CCT. Due to the large mass and hydrophobicity of FACT, tablets are hand crushed prior to dissolution. This is accomplished by simply folding the tablet in weighing paper and striking it with a pestle until the largest pieces measure approximately 3 to 5 mm. A comparison of dissolution rates of whole tablets, tablets cut in four to five pieces, and hand-crushed tablets showed that dissolution using non-whole tablets to be the best with respect to release of Famotidine. The dissolution rates of tablets crushed with a pestle (until the largest pieces measure approximately 3 to 5 mm) between a folded piece of weighing paper was *"relatively"* equivalent to tablets cut into four or five pieces. About 100% of the Famotidine was dissolved in 45 minutes. Whole tablets dissolved much more slowly, with only —% Famotidine dissolved after 45 minutes and —% dissolved after 60 minutes.

The specifics of the dissolution method used are as follow:

Table 15. Dissolution Method for FACT

Apparatus II	Paddles
Speed	100 RPM
Dissolution medium	0.1M Acetate buffer (pH 4.5)
Volume	900 ml
Temperature	37°C ±0.5°C

CHEMISTRY

The composition characteristics of the to-be-marketed 10-mg FACT and the reference 10-mg FCT, were compared. Based on the data submitted, it was found that both of these tablets were compositionally proportional with respect to the active ingredient, Famotidine.

COMPONENT-COMPONENT INTERACTIONS

Variations in Famotidine absorption rate and/or antacid efficacy onset and duration may occur in the proposed marketable tablet (FACT), as compared to when given concurrently but in separate tablets. These effects are hinted to by the results of one bioavailability study (Protocol 101) in which subjects were dosed in a fasted state. The calculated T_{max} for FCT (10 mg Famotidine alone) was 1.8 hours, which was statistically different than that for FACT (sponsor proposed marketable tablet) 2.4 hours. In this case, the observed T_{max} difference for Famotidine from FACT may be due to the presence of the antacid in the gastrointestinal lumen, which may have changed the characteristics of the gastrointestinal pH and/or lining, hence possibly affecting the absorption rate of Famotidine. Additionally, the T_{max} difference may be the result of formulation and/or manufacturing process difference for the two tablets (*i.e.* FCT and FACT), which resulted in different disintegration or dissolution characteristics between the tablets. Under CFR 21, Part §320.25.g.1 the following is stated:

> *"Generally, the propose of an in vivo bioavailability study involving a combination drug product is to determine if the active drug ingredient or therapeutic moiety in the combination drug product is equivalent to the rate and extent of absorption of each active drug ingredient or therapeutic moiety administered concurrently in separate single-ingredient preparations."*

In essence, in this submission, it is noted that neither the clinical studies nor the bioavailability studies had a treatment where the 10-mg Famotidine tablet and the antacid tablet were given concurrently. The four different regimens to which the subjects and/or patients were subjected to in these studies were FACT (10-mg Famotidine + 21.5-mEq ANA), FCT (10 mg Famotidine), ANC (21.5-mEq), and Placebo (PBO).

PHARMACODYNAMIC PARAMETERS

Four pharmacodynamic parameters were assessed in study Protocol 098. These were 1) Mean Area Under the Intra-esophageal pH *vs.* Time Curve: 0 to 60 minutes Post-dose; 2) Mean Area Under the Intra-gastric pH *vs.* Time Curve: 0 to 60 minutes Post-dose; 3) Mean Area Under the Intra-gastric pH *vs.* Time Curve: 5 to 9 hours Post-dose; 4) Reflux Episodes: 0 to 60 Minutes Post-dose. The treatments comparisons were FACT *vs.* FCT; FACT *vs.* ANC; FACT *vs.* PBO; FCT *vs.* PBO; ANC *vs.* PBO; and FCT *vs.* ANC. The results of the assessed PD parameters and the treatment ratios or comparisons are summarized in the following tables:

Table 9. Obtained pH measurements.

Group	Intra-esophageal 0-60 min. (Geo. Mean)	Intra-gastric 0-60 min. (Geo. Mean)	Reflux episodes 0-60 min (LS Mean).	Intra-gastric 5-9 hrs. (Geo. Mean)
FACT	*5.99*	*3.02*	*1.96*	*1.68*
FCT	*5.19*	*2.44*	*4.76*	*1.52*
ANC	*6.00*	*3.10*	*2.57*	*0.69*
PBO	*5.11*	*2.68*	*5.39*	*0.70*

Table 10. Intra-esophageal pH 0-60 minutes post-dose:

Group	Geometric Mean	95% CI	Increase	p-Value
FACT/FCT	1.15	1.09, 1.22	15%	<0.001
FACT/ANC	1.00	0.95, 1.05	0%	0.931
FACT/PBO	1.17	1.11, 1.24	17%	<0.001
FCT/ANC	1.16	1.10, 1.22	16%	<0.001
FCT/PBO	1.02	0.96, 1.07	2%	0.554
ANC/PBO	1.17	1.11, 1.24	17%	<0.001

Table 11. Intra-gastric pH, 0-60 minutes post-dose:

Group	Geometric Mean	95% C.I.	Increase	p-Value
FACT/FCT	1.24	1.04, 1.48	24%	0.018
FACT/ANC	0.98	0.82, 1.17	-2%	0.781
FACT/PBO	1.13	0.95, 1.35	13%	0.176
FCT/ANC	1.27	1.07, 1.52	27%	0.009
FCT/PBO	0.91	0.76, 1.09	-9%	0.291
ANC/PBO	1.16	0.97, 1.38	16%	0.105

Table 12. Intra-gastric pH, 5-9 hours post-dose:

Group	Geometric Mean	95% C.I.	Increase	p-Value
FACT/FCT	1.10	0.86, 1.42	10%	0.442
FACT/ANC	2.45	1.90, 3.15	145%	<0.001
FACT/PBO	2.41	1.87, 3.09	141%	<0.001
FCT/ANC	2.22	1.73, 2.86	122%	<0.001
FCT/PBO	2.18	1.70, 2.81	118%	<0.001
ANC/PBO	0.98	0.76, 1.26	-2%	0.891

Table 13. Reflux episodes, 0-60 minutes post-dose:

Group	LS Mean	95% C.I.	p-Value
FACT/FCT	-2.80	-4.30, -1.30	<0.001
FACT/ANC	-0.61	-2.11, 0.89	0.420
FACT/PBO	-3.42	-4.93, -1.92	<0.001
FCT/ANC	-2.19	-3.69, -0.69	0.005
FCT/PBO	-0.63	-2.13, 0.88	0.408
ANC/PBO	-2.81	-4.32, -1.31	<0.001

PHARMACOKINETIC PARAMETERS AND BIOEQUIVALENCY

A summary of the calculated PK parameters (means with SD, and ranges) for all treatments from selected studies in this NDA submission is given in the following table. For the bioequivalency analysis, the 90% confidence intervals using the two one-sided test procedure for all three treatments was followed. Study and each of the treatments within each study are presented in this summary.

Table 14. Summary table for the Bioequivalence/Bioavailability studies.

		Protocol 095*			Protocol 096**			Protocol 101***		
		FACT		FCT	FACT		IV	FACT		FCT
AUC_{0-24} *ng.hr/ml*	*Mean*	252.10		243.77	228.64		429.33	277.8		296.7
	Range									
	±SD	51.3		52.6	49.61		72.68	80.5		84.9
	CV									
	Mean Ratio		1.03			0.53			0.94	
	90% CI		0.99 – 1.09			0.48 – 0.60			0.86 – 1.01	
C_{max} *ng/ml*	*Mean*	37.13		38.57	38.7			49.8		53.8
	Range									
	±SD	6.6		8.3	9.5			15.4		17.8
	CV									
	Mean Ratio		0.96						0.93	
	90% CI		0.91 – 1.02						0.84 – 1.02	
t_{max} *hr*	*Mean*	2.90		2.86	2.5			2.4		1.8
	Range									
	±SD	0.5		0.7	0.7			0.8		0.7
	CV									
	Mean Ratio		0.04						0.53	
	90% CI		-0.26 – 0.33						0.11 – 0.94	
$t_{1/2}$ *hr*	*Mean*									
	Range									
	±SD									
	CV									
	Mean Ratio									
	90% CI									

* Protocol 095: standard FDA breakfast, day time.
** Protocol 096: fasted state, day time.
*** Protocol 101: fasted state, day time.

SAFETY

All submitted studies had no serious adverse events reported nor deaths directly related to the drug administered.

LABELING

The labeling section of the submission uses the previously approved text under NDA #20-235 for PEPCID AC Acid Controller and conforms to the current Code of Federal Regulations regarding Antacid Products for OTC use (21 CFR 331). The following are some of the changes made by the sponsor in proposed label insert:

- A DRUG INTERACTION PRECAUTION was added per 21 CFR 331.30(d) for OTC Antacid Products.
- The title of the section, **"How to use Pepcid AC Acid Controller"** has been changed to **"How to use Pepcid** ——.
- In the section, **"Proven effective in clinical studies"**, the first sentence is new and provides information derived from several clinical studies.
- In the section, **"Proven effective in clinical studies"**, the information contained in the "Onset of Relief" and "Duration of Relief" graphs and the corresponding titles is new and was derived from a clinical study.
- The Statement of Identity is new and is a combination of the Statement of Identity approved for PEPCID AC Acid Controller and 21 CFR 331.30 (a) for OTC Antacid Products.

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- The DRUG INTERACTION PRECAUTION was added per 21 CFR 331.30(d) for OTC Antacid Products.

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CONCLUSIONS

I) *Pharmacokinetics*:

1) The to-be-marketed 10-mg Famotidine/21.5-mEq antacid Chewable Tablet (FACT), was found to be bioequivalent to the marketed 10-mg Famotidine Chewable Tablet (FCT) for C_{max} and $AUC_{0-24hrs}$. This was assessed in two separate studies, protocols 095 and 101, using the two-one-sided t-test and 90% Confidence Interval method. Both of these studies were performed during the day-time, but one was under fed conditions (Protocol 095) while the other was under fasting conditions (Protocol 101).

2) In Protocol 101, day-time fasted-state study, the T_{max} for FCT was statistically significantly shorter than for FACT, 1.8 hrs and 2.4 hrs respectively, approximately 35 minutes. In Protocol 095, day-time fed-state, the T_{max} for FCT and FACT were relatively

the same, 2.9 hrs. The difference in FACT and FCT T_{max} can probably be attributed to the fact that the individuals in study protocol 101 were in a fasted state while in protocol 095 they were fed a FDA standard breakfast prior to dosing. The calculated T_{max} for FACT in all three studies, protocols 095, 096, and 101 (two fasted and one fed state, respectively) were, 2.9 hrs, 2.5 hrs, and 2.4 hrs respectively. The calculated T_{max} for FCT in Protocols 095 (fed state) and 101 (fasted state) were statistically significantly different, 2.9 and 1.8 respectively.

i) The "*time of the sample in which the maximum measured plasma* Famotidine *concentration occurred*" or T_{max} from study protocol 101, suggest that there is a quicker exposure to Famotidine (*i.e.* mean of 36 minutes) when given alone, as compared to Famotidine given concomitantly with an antacid under fasting conditions.

3) In all three pharmacokinetic studies (Protocols 095, 096, and 101) and the pharmacodynamic study (Protocol 098), the subjects were told to "chew" the FACT tablets for an unknown length of time and to swallow the remains with water (120-ml in PK studies 095, 096, 101; and 60-ml in PD study 098). This may be another source of variability in the calculated PK parameters in all four studies.

II) *Pharmacodynamics*:

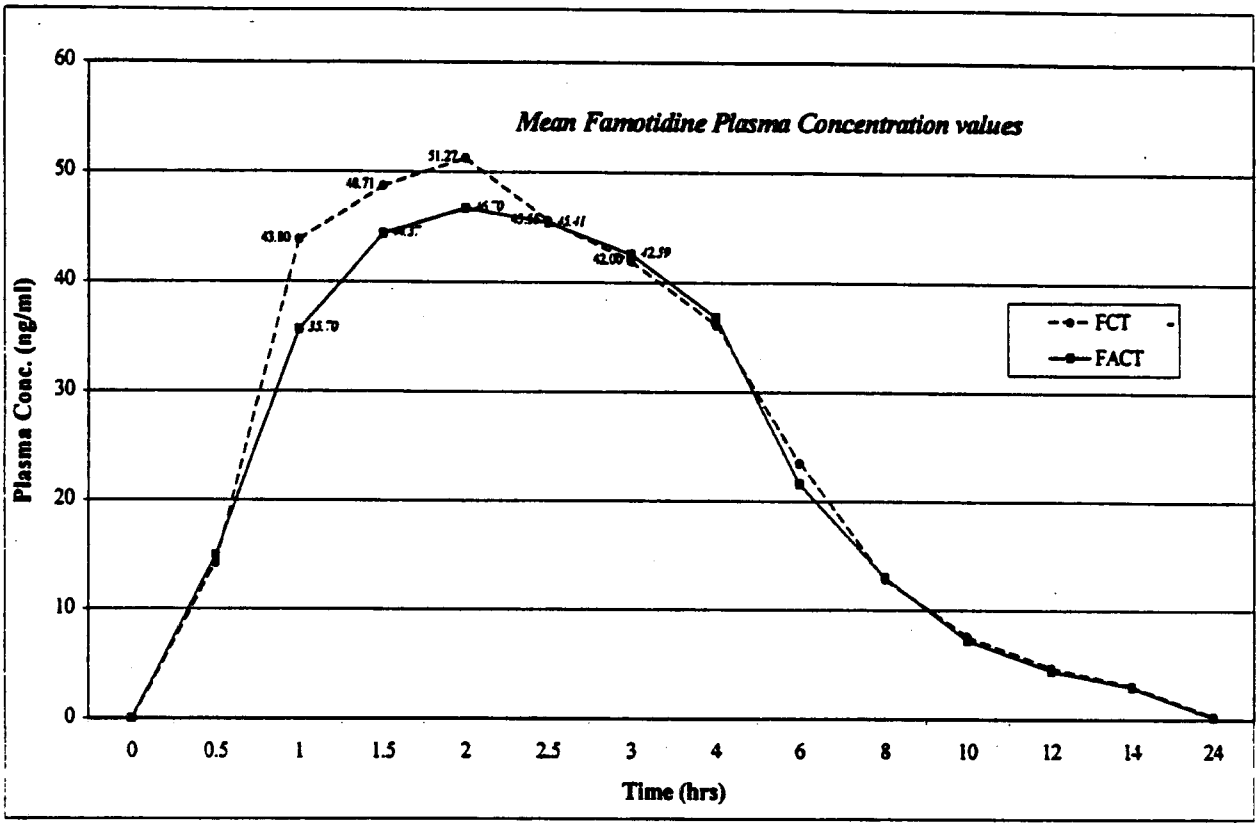
1) In the pharmacodynamic study Protocol 098, intra-gastric pH was measured at 30-minute intervals, subjects were given one of the four treatments (FCT, FACT, 21-mEq ANC, or Placebo) 1-hour after they had finished a high-fat evening meal. The mean intra-gastric pH for the 5-9 hr post-dose period was significantly greater in the FACT and FCT treatments as compared to the ANC and PBO (Placebo) treatments. The measured mean intra-gastric pH for the ANC and PBO tablets were lower than FACT or FCT, but similar to each other during the 5-9 hr post-dose period. Likewise, the measured mean intra-gastric pH for the FACT and FCT tablets were similar to each other during the 5-9 hr post-dose period.

2) In the pharmacodynamic study, Protocol 098, intra-esophageal pH and number of reflux episodes were used to assess the efficacy of FACT over FCT in the first 60-minutes post-dose. The number of reflux episodes, as defined by the sponsor, were significantly less with FACT and ANC treatments than with FCT or PBO treatments, as noted in Table 9 of this review. The means for the intra-esophageal and intra-gastric pH were 1.0 and 0.5 pH units, respectively, higher for FACT or ANC treatments compared to FCT and PBO treatments, also noted in Table 9 of this review.

III) *PK/PD*:

1) There is a delay in FACT to reach Famotidine T_{max}, as compared to FCT (2.4 and 1.8 hr, respectively) under fasting conditions (Study Protocol 101), which may be of concern and have clinical significance. This 36-minute difference of FACT and FCT T_{max} occurs between the 1 to 3 hour time points, well after the presence and therapeutic effect of any co-administered antacid has occurred. This may lead to a decrease of intra-gastric pH and an incidence of reflux during this time frame, which could also lead to patients re-dosing themselves prior to the original Famotidine dose reaching T_{max}. This is of particular concern during the day time in which there are many stimuli sources for acid secretion.

Figure 2. Mean Famotidine Plasma concentration values at each time-point, Protocol 101.



IV) *Unknown PK & PD drug-product characteristics:*

Based on the information provided by the sponsor in this submission, we can not ascertain the following PK/PD characteristics of FACT as compared to FCT:

1) The to-be-marketed drug-product, FACT, PK profile (AUC, C_{max}, and T_{max}) for night time taken with a standard high-fat meal.
2) The to-be-marketed drug-product, FACT, PK profile (AUC, C_{max}, and T_{max}) for night time 1-hour after a standard high-fat meal.
3) The to-be-marketed drug-product, FACT, PK profile (AUC, C_{max}, and T_{max}) for night time under strict fasting conditions.
4) The to-be-marketed drug-product, FACT, PD assessment for night time under strict fasting conditions.
5) The to-be-marketed drug-product, FACT, PD assessment for night time taken with a standard high-fat meal.
6) The to-be-marketed drug-product, FACT, PD assessment for day time taken with a standard high-fat meal.

7) The to-be-marketed drug-product, FACT, PD assessment for day time 1-hour after a standard high-fat meal.

8) The to-be-marketed drug-product, FACT, PD assessment for day time under strict fasting conditions.

V) *Drug-Drug interaction:*

1) The sponsor did not conduct any studies to characterize any potential interactions with other drugs. The sponsor states that past studies with Famotidine in humans, in animals, and in-vitro have shown no significant interference with the disposition of drugs metabolized by the hepatic microsomal enzymes, *e.g.* cytochrome P-450.

2) It is also known that the concomitant administration of antacids can reduce the absorption of a variety of drugs, *e.g.* tetracycline. The sponsor did not conduct any studies in which the pharmacokinetic parameters or the pharmacodynamic assessment of FACT treatment -as compared to FCT and ANC treatments simultaneously given- could be determined. The sponsor did provide a reference material (#17 of submission, Sullivan, *et. al.* Aliment. Pharm. Ther. 8(1): 123-126, 2/94) in which the effect of a commercially available antacid (Mylanta Double Strength, 30-ml) was co-administered to several H_2-receptor antagonist, including 40-mg Famotidine. This reference concludes that the co-administered liquid antacid negatively affect the AUC and Cmax of 40-mg Famotidine, by 24% and 19% respectively. It also states that in this same referenced study report, the changes in T_{max} for the 40-mg Famotidine were statistically not significant.

3) Variations in Famotidine absorption rate and/or antacid efficacy onset and duration may occur in the proposed to-be-marketable tablet (FACT), as compared to concurrently but in separate tablets (FCT + ANC). These effects are hinted to by the results of the bioavailability study Protocol 101, in which subjects were dosed in a fasted state (Figure 1 of this review). The calculated T_{max} for FCT (10 mg Famotidine) was 1.84 hours which was statistically (p=0.563) different than that for FACT (to-be-marketable tablet) 2.36 hours. This may be of concern for at approximately the same time the effect of the antacid used in these studies has diminished or is not existent, as demonstrated by the lowering of the intra-gastric pH in Figure 1.

VI) *Adverse event*:

1) There are no reported serious adverse events in any of the bioequivalency studies submitted by the sponsor.

VII) *Dissolution method*:

The sponsor provided a description of the dissolution method and assay methods used to test stability of the new drug product. The description of the procedure included separate assay methods for the Famotidine and Antacid portions of the drug product that are based on a USP method. The drug product is "hand crushed to small size particles" and placed in 900-ml (pH 4.5) of dissolution media with a paddle rotating at 100 rpm at 37°C, resulting in a Q= ——at 45-minutes.

The in-vitro dissolution method presented for FACT is a modification of that used for the already approved 10-mg Pepcid CCT. FACT contains the same coated famotidine ——— particles as Pepcid CCT. A comparison of dissolution rates of whole tablets, tablets cut in four to five pieces, and hand-crushed tablets showed that the dissolution using non-whole tablets to be the

best with respect to release of famotidine. In whole tablets, about —% of the famotidine was dissolved after 45-minutes and —% dissolved after 60-minutes.

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmacological Evaluation II has reviewed the information and data submitted February 23, 1998 with NDA 20-958. Based upon an evaluation of the provided information and data it is concluded that:

1. The new 10-mg Famotidine/Antacid Chewable Tablet (FACT) in its to-be-marketed formulation, is equivalent in extent of absorption (*i.e.* C_{max} and $AUC_{0\text{-}24hrs}$) to the reference marketed 10-mg PepcidAC Acid Controller Film-Coated Tablet (FCT), both in the fed and fasted states during day time. During day time and under fasting conditions, the differences in the mean-time-to-peak-concentration (T_{max}) for the 10-mg FACT versus 10-mg FCT is approximately 35 minutes. It is recommended that the reviewing medical officer be made aware of the T_{max} difference between FACT and FCT and determine whether this difference in T_{max} is clinically significant.
2. With respect to the in-vitro dissolution method used for this drug product as described in this submission, the office of Clinical Biopharmaceutics suggests that a new set of specifications (see table below) be applied to the all batches of this drug product. Once the new specifications are agreed upon, testing of the drug product batches used in these studies would need to be resubmitted. The use of "hand-crushed" or "4-5 pieces" of tablets is not considered to promote an accurate and reproducible dissolution test. Instead, the use of whole tablets in the dissolution test would be a more accurate and provide a reproducible method, with less intrinsic variability.

Suggested dissolution method for FACT

Formulation	Whole Tablet
Apparatus II	Paddles
Speed	50 RPM
Dissolution medium	0.1M Acetate buffer (pH 4.5)
Volume	900 ml
Temperature	37°C ±0.5°C
Q	—
Time	45-minutes

/S/

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Concurrence:

/S/

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Cc: HFD-160 NDA 20-958 (1x); DIV.FILE (1x); FOLKENDT (1X); SANCHO (1X); HUNT (1X); LEED (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 LLESKO
CDR Attn.: Barbara Murphy

Enclosures: [Click here and type number]

Attachments