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APPLICATION NUMBER: 020752

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

JUL 30 1997

Clinical Pharmacology and Biopharmaceutics Review

NDA 20-752

Submission Date: 8-1-96, 10-11-96, 1-3-97 and 2-11-97

PEPCID RPD™

Famotidine Wafers: 20 and 40 mg

Sponsor: Merk and Co., Inc.
P.O. Box 4, BLA-20
West Point, PA 19486-0004

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Priority:1S

Reviewer: Rajendra S. Pradhan, Ph.D.

Type of Submission: New Formulation

Synopsis:

Famotidine (FM) is currently marketed in the U.S. as intravenous injection 10 mg/ml (approved on 11-4-1986), powder for reconstitution for oral use 40 mg/5 ml (approved on 2-2-1987) and tablet for oral use 20 and 40 mg (approved on 10-15-1986). Famotidine is indicated for short term treatment of active duodenal ulcer, maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer, short term treatment of active benign ulcer, short term treatment of gastroesophageal reflux disease and treatment of pathological hypersecretory conditions such as Zollinger-Ellison Syndrome. In this application the sponsor is requesting approval to a new dosage form of FM, famotidine wafer. According to the sponsor this dosage form will provide the patients an option of an alternate dosage form that rapidly dissolves on the tongue and can be taken without water.

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The sponsor has conducted a satisfactory study to show bioequivalence (BE) between 40 mg approved tablet formulation (reference) and 40 mg round-shaped wafer (test). The sponsor is requesting an approval of this new dosage form based solely on this BE study. In other words, the sponsor has not performed any clinical safety-efficacy trial for this new dosage form. The sponsor is also asking a waiver for bioavailability requirements study for 20 mg wafer

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FM wafer 40 mg formulation used in the BE study differed in composition compared to the proposed to-be-marketed FM wafer 40 mg formulation. However, the differences in the shape of wafers, the packaging materials

Therefore, the proposed to-be-marketed formulation, 40 mg, could be considered as bioequivalent to FM wafer 40 mg formulation used in the BE study.

Therefore, the Div. of

Pharmaceutical Evaluation-II, OCPB would like to grant a waiver for bioavailability requirements for the 20 mg wafer.

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Background

Famotidine dosage forms currently available on the market for prescription use include the 20 and 40 mg tablet the 10 mg/mL i.v. injections in 2 mL and 4 mL formulations, the 20 mg/50 mL i.v. premixed injection, and the 40 mg/5 mL oral suspension. The sponsor is proposing to market a wafer formulation of famotidine.

It disintegrates rapidly on the tongue, and provides a formulation that is convenient and easy to take. The new hexagonal-shaped wafer formulation has been developed as an alternate dosage form to the formulation. Two strengths of the formulations are proposed in this application: the 20 and the 40 mg wafers.

The wafer formulation is also referred to in this application as RAPIDISC (RPD), ZYDIS™.

Formulation:

Table 1 lists the composition of the proposed wafer dosage form.

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Table A-1. Composition (mg) of the proposed 20 and 40 mg hexagonal-shaped Famotidine Wafer Formulations.

Composition	20 mg Wafer	40 mg Wafer	Function
Famotidine			
Gelatin			
Mannitol			
Xanthan Gum			
Aspartame			
Mint Flavor			
Red Ferric Oxide			
Total Wafer Weight (mg)			

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Table 2.1. Table 2 Composition (mg) of the 40mg round-shaped wafer formulation used in the bioequivalency study.

Ingredient	40 mg Wafer
Famotidine	
Gelatin	
Mannitol	
Xanthan Gum	
Aspartame	
Mint Flavor	
Red Ferric Oxide	
Total Wafer Weight (mg)	

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Famotidine wafers were originally developed as
unique appearance to the proposed wafer product

The composition of the proposed 40 mg

wafers. To give a

wafer was revised so that the

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Drug Product Dissolution

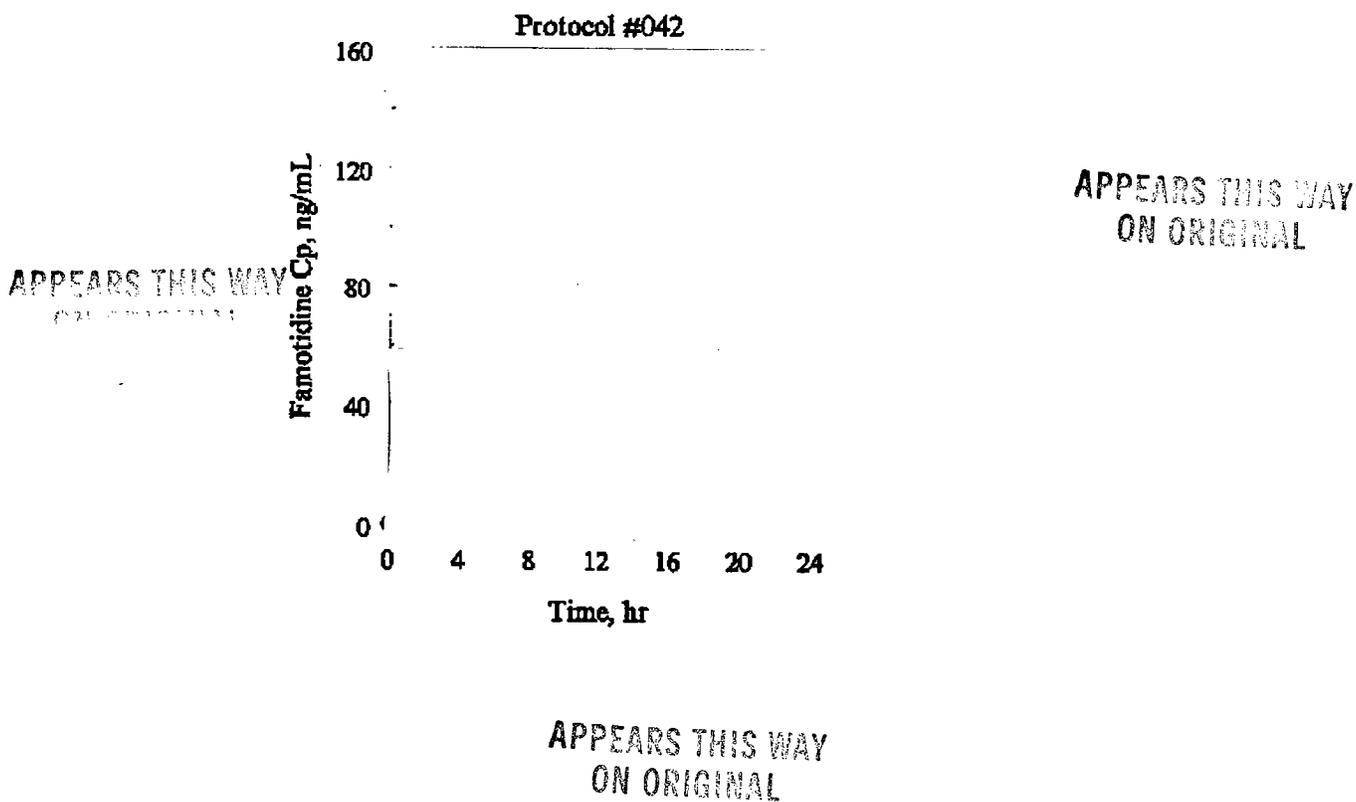
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Bioavailability of the 40 mg wafer formulation

A randomized, open, two-way crossover study was conducted in 18 healthy male subjects to investigate the bioequivalence of the 40 mg wafer to the 40 mg tablet. The treatment A was 40 mg famotidine tablet given with 120 ml of water. The treatment B was 40 mg FM wafer administered without water and subjects were not allowed to drink water for 1.5 hr postdose. Plasma samples were collected and assayed for FM using a validated method. Following are the mean plasma concentration versus time profile for treatments A and B.

Figure 1



The following table summarizes the PK parameters and bioequivalence analysis.

Parameters	Wafer	FCT
AUC ng.h/ml (geo. mean)	1096.4	1041.4
Ratio (Wafer/FCT)	1.05	
90% CI (Wafer/FCT)	(0.96, 1.15)	
Cmax ng/ml (geo. mean)	161.1	168.1
Ratio (Wafer/FCT)	0.96	
90% CI (Wafer/FCT)	(0.85, 1.08)	

Based on the AUC and Cmax comparison round shaped 40 mg wafer formulation was bioequivalent to the 40 mg FM. However, the mean Tmax of the wafer formulation was delayed by about 0.9 hr as compared to the (median difference = 1.0 hr). The sponsor has presented a pharmacokinetic-pharmacodynamic (PK-PD) analysis¹ to support that difference seen in Tmax is clinically insignificant. This PK-PD analysis shows that a plasma FM steady state concentration of produces a 50% reduction in IV pentagastrin-stimulated gastric acid secretion (IC₅₀). If one compares the time for which the mean plasma concentration stays above IC₅₀ from this bioequivalence study, the 40 mg wafer show greater duration of action than FM by 1 to 2 hours. The clinical impact of this difference at the steady state (chronic treatment) may be small. However, it should be noted that the clinical significance of this difference in Tmax should be judged by the Medical Officer (HFD-180).

When the concentration-time data for and wafer were fitted to a one compartmental model the mean difference between the estimated Tmax values was 0.45 h (as oppose to 0.9 h, determined using the non-parametric approach). When steady state concentration profile was simulated using the model information (Figure 2), the difference in the mean concentration profiles of the two formulation appear minimal. It should be noted that Tmax estimation is dependent on the sampling strategy.

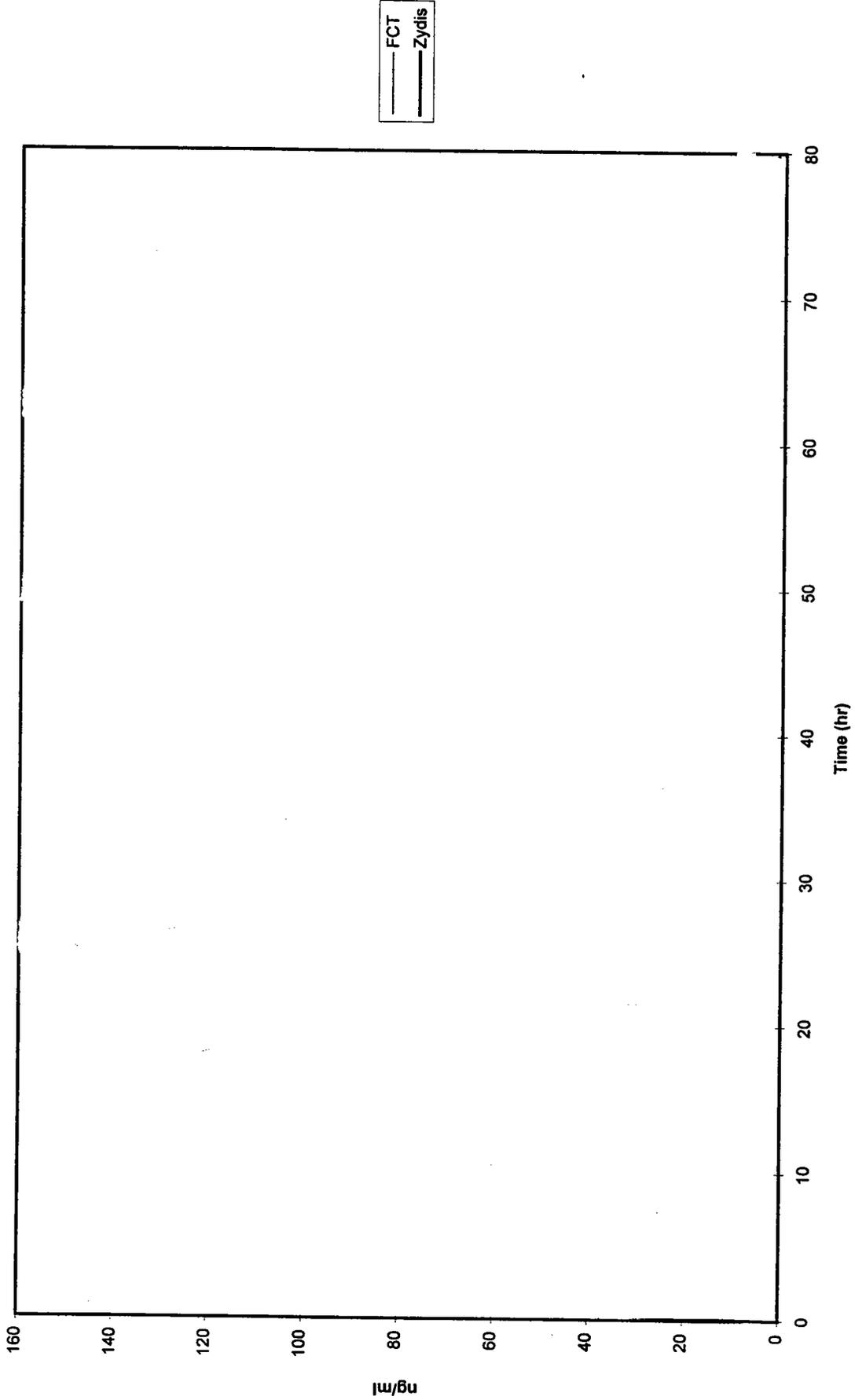
In the bioequivalence study, the wafer batch size was only significantly smaller than the . The proposed production batch size Thus, the biobatch was greater than 10% of production batch However, it is noted that

The usual size of batch is

¹ De Gara C. J., Burget D. W., Chremos A. N., Silletti C., Hunt R. H. The effects of IV famotidine on pentagastrin-simulated gastric secretion in man. *Aliment Pharmacol Ther*, 1: 125-132 (1987)

SS_SIM Chart 1

40 mg Famotidine BID/Mean Simulated Conc.



wafers.

Pharmaceutical Evaluation II, OCPB

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