CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020902

MEDICAL REVIEW(S)

C50/F5/Kurdt

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

AUG - 6 1998

AUG - 6 1998

NDA:	20-902
Sponsor:	Merck Research Laboratories
Drug name:	Nonprescription Famotidine Gelatin Coated Tablets (Pepcid AC Acid Controller Gelcap), 10mg
Date submitted:	September 30, 1997
Date received:	October 1, 1997
Review completed:	August 5, 1998
Reviewer:	Kathy M. Robie-Suh, M.D., Ph.D.

Background:

Pepcid AC Acid Controller (famotidine 10mg as a film-coated swallow tablet) currently is marketed over-the-counter for treatment and prevention of heartburn symptoms (initial approval 4/28/95). In this submission the sponsor proposes a gelatin-coated tablet (gelcaps) formulation of famotidine 10mg as an alternative dosing form for the currently approved over-the-counter famotidine indications. The sponsor claims efficacy of the new formulation based on demonstration of bioequivalence to the already approved film-coated tablet product. A supporting bioequivalence study is included in this application.

Materials Reviewed:

This submission consists of the following:

Vol. 1.1	Index, Synopsis of Application, including Annotated Labeling
Vols. 1.2 through 1.5	Chemistry, Manuracturing and Controls Documentation
Vol. 1.6	Human Pharmacokinetics and Bioavailability Documentation
Vols. 1.7	Clinical Documentation
Vols. 1.8	Statistical Documentation
Vol. 1.9	Case Report Form Tabulations

Because efficacy for the gelatin-coated tablet formulation is being claimed based on bioequivalence of the chewable formulation to the already marketed film-coated tablet formulation, no clinical evidence for efficacy is presented in this submission. There is one clinical study reported in full in this submission, namely Study #085, a pharmacokinetic/bioequivalence study, which was reviewed by FDA Biopharmaceutics and found to adequately demonstrate bioequivalence of the 10mg gelcap formulation to the currently marketed 10mg film-coated tablet. (See FDA Clinical Pharmacology and Biopharmaceutics Review dated 7/27/98).

No other clinical studies have been submitted in this application.

This submission contains no case report forms, because no patients died or were discontinued from study because of adverse events.

For this review I have examined information in volumes 1.1, 1.6 and 1.9.

Chemistry, Manufacturing and Control Information:

The compositions of the proposed gelcap formulation of OTC famotidine is shown in the table below:

Composition of Proposed Famotidine 10mg Gelcaps Formulation

Ingredients	mg/tablet	Function
[redacted]		
Famotidine [redacted]	10.0	[redacted]
Pregelatinized starch [redacted]	[redacted]	
Microcrystalline Cellulose [redacted]		
Magnesium Stearate [redacted]		
Talc [redacted]		
[redacted] Core tablet weight:		
Hydroxypropyl Methylcellulose [redacted]		
Castor Oil [redacted]		
[redacted] Subtotal:		
[redacted]		
Sodium Lauryl Sulfate [redacted]		
[redacted]		
[redacted]		
[redacted] Total weight:		
[redacted]		

Clinical Pharmacology:

Famotidine is a competitive histamine H_2-receptor antagonist. It inhibits basal and nocturnal gastric acid secretion and food or pentagastrin induced gastric acid secretion in normal people and in hypersecretors.

Famotidine exhibits linear pharmacokinetics over the dose range studied (5 to 40mg). About 71% of an intravenous dose of famotidine appears unchanged in the urine. Upon oral administration, about 38% of the dose is found in the urine and 51% in the feces. The only identified metabolite of famotidine is the S-oxide. The half-life following intravenous or oral adm

inistration is about 2.8 hours in healthy young individuals. The half-life increases disproportionately with renal impairment.

Bioavailability of famotidine from prescription dose Pepcid tablets (20mg and 40mg) is about 42%. Famotidine is not extensively bound to plasma protein. Famotidine does not have a high affinity for interaction with cytochrome P-450 and does not significantly affect the pharmacokinetics of drugs (such as diazepam, theophylline, and phenytoin) metabolized by cytochrome P-450 systems.

Bioequivalence Study 085 showed the proposed 10mg gelcap to be bioequivalent to the marketed film-coated tablet (FCT) formulation. This was a single-dose, randomized 2 period cross-over study in 24 normal subjects. Results of this study are summarized in the following table:

Study 085: Results of Bioequivalence Study

	Gelcap	Film-Coated Tablet	Ratio (Gelcap/FCT)
Geometric mean AUC (ng.hr/mL)	197.5	184.6	
Relative bioavailability (ratio of geometric mean AUC gelcap/FCT) (90% CI)			1.07 (0.96, 1.19)
Geometric mean C_{max} (ng/mL)	31.7	28.9	
ratio of C_{max} (gelcap/FCT) geometric means (90% CI)			1.10 (0.97, 1.24)
Mean $T_{max} \pm$ SD (hr)	2.2 ± 0.7	2.4 ± 1.1	

90% CI = 90% confidence interval
SD = standard deviation

based on sponsor's table, NDA Vol. 1.1, p. 02-000181; Vol. 1.7, p. 08-000298

Clinical Safety Summary:

Clinical investigations of famotidine gelcaps include only Study 085, the bioequivalence study which was described above. A total of 24 healthy adult subjects (14 males, 10 females) received a single dose of famotidine 10mg gelcap and famotidine 10mg film-coated tablet in this study. Subjects were aged 20-40 years (mean, 27.6 years; median, 26 years). About 71% of subjects were Caucasian, 12.5% were Hispanic, 12.5% were Asian and 4.2% were Black. The most common pre-existing condition in the subjects was allergy of some sort (7 subjects). There was no use of concomitant medications during the study. A total of 4 non-serious adverse events were reported during the study. These were: ecchymosis on the arm in one subject between treatment periods; mild dizziness (lightheadedness) in one subject after receiving famotidine 10 mg Gelcap; moderate headache in one subject between treatments, and mild nausea in that same subject after receiving famotidine 10 mg gelcap. The dizziness was considered possibly related to study drug. The other events were considered probably not or definitely not related to study drug. There were no serious events; there were no deaths. All 24 subjects completed the study. No clinical laboratory studies were done during this study.

[Note: There are some minor discrepancies between the patient characteristics summarized in the Safety Summary and those in the study report. These appear likely to be typographical errors. I have used the information in the data tabulations].

The safety of famotidine 10mg gelcaps is further supported by the safety information for the famotidine 10mg film-coated tablet (NDA 20-325). (See my Medical Officer's Reviews dated 1/12/94 and 6/13/94).

Also, by my review of the FDA Adverse Drug Reaction Information System (ADRIS) data for all famotidine products, though there was a large increase in spontaneous adverse event reports in the year following approval of famotidine for OTC marketing (3495 reports in 1996 as compared to 295 reports in 1995) [most likely reflecting the increased number of people taking famotidine since the drug was made available OTC], the numbers of serious adverse events increased only mildly (70 in 1995 and 84 in 1996). In the overall database the most frequent adverse events were "no drug effect" (928 reports, 13.0% of all reports), diarrhea (579 reports, 8.1% of all reports), abdominal pain (365 reports, 5.1% of all reports), constipation (347 reports, 4.9% of all reports), and rash (335 reports, 4.7% of all reports).

Reviewer's Comments and Discussion:

The famotidine 10mg gelcaps formulation was well-tolerated in the clinical study in which it was used (bioequivalence Study 085 in 24 adult males and females). Also, it has been demonstrated to be bioequivalent to the already marketed film-coated tablet. (See Biopharm review dated 7/29/98). The safety database for famotidine 10mg is adequate to support the marketing of the proposed gelcaps formulation of famotidine.

The sponsor has provided annotated labeling for the gelcaps. The labeling for the gelcaps product should be the same as for the marketed film-coated tablet formulation, except that:

- the dosing instruction should say: "Swallow one gelcap with water."
- information about the chemical composition of the gelcaps should be included.
- A statement in the Clinical Studies section should indicate that the gelcaps have been shown to be bioequivalent to the film-coated swallow tablets.

These modifications have been made by the sponsor in the proposed labeling.

Conclusions and Recommendations:

From a clinical point-of-view I recommend that the proposed application be approved.

The labeling for the gelcaps should be essentially the same as for famotidine 10mg film-coated tablets (with modifications as indicated under the bulleted points above). Also, recommendations for labeling from the Division of Over-the-Counter Drug Products should be considered. (See Labeling Review, by G. Chang, Division of OTC Drug Products, signed 7/27/98).

/S/ [redacted]

Kathy M. Robie-Suh, M.D., Ph.D. 8/6/98

Concur. 08/06/98

/S/ [redacted]

cc:
NDA 20-902
HFD-180
HFD-180/LTalarico
HFD-180/KRobie-Suh