

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-325 / S-015

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-325 SUPPL # 015
Trade Name Pepcid Generic Name famotidine

Applicant Name Merck HFD-560

Approval Date September 23, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/___/ NO /X/

b) Is it an effectiveness supplement? YES /X/ NO /___/

If yes, what type(SE1, SE2, etc.)? SE2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES / / NO / /

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #20-325

NDA #20-801

NDA #20-902

NDA #20-958

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO / ___ /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES // NO //

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES // NO //

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES // NO //

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/NO /_X_/

If yes, explain:

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 114

Investigation #2, Study # 117

Investigation #3, Study # 128

Investigation #4, Study # 017

Investigation #5, Study # 019

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /_X_/

Investigation #2	!	
	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
	!	
_____	!	_____
	!	
_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X___/

If yes, explain: _____

 Signature of Preparer
 Title:

Date

Signature of Office or Division Director

Date

cc:
 Archival NDA
 HFD- /Division File
 HFD- /RPM
 HFD-610/Mary Ann Holovac
 HFD-104/PEDS/T.Crescenzi

Form OGD-011347
 Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Curtis Rosebraugh
9/26/03 03:33:10 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 20-325 Supplement Type (e.g. SE5): SE2 Supplement Number: 015

Stamp Date: 11/22/02 Action Date: 9/23/03

HFD 560 Trade and generic names/dosage form: Pepeid (famotidine) 20mg Maximum Strength

Applicant: MERCK Therapeutic Class: Acid Reducer

Indication(s) previously approved: Prevention and Treatment of Heartburn

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Prevention of Heartburn

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

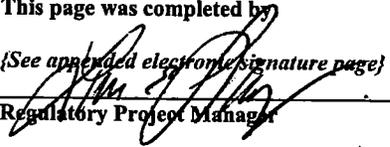
Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by

{See appended electronic signature page}


Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Treatment of Heartburn

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

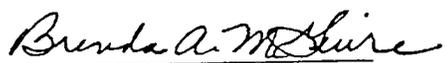
/s/

David Hilfiker
10/27/03 12:03:50 PM

Nonprescription Famotidine 20 mg
Item 16 – Debarment Certification

1

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.



Brenda A. McGuire,
M.S., R.N.
Associate Director
Worldwide OTC Regulatory Affairs

11/22/02
Date

Nonprescription Famotidine 20 mg
Item 17 – Field Copy Certification

1

Pursuant to 21 CFR 314.50(k)(3), a complete field copy of the Chemistry, Manufacturing and Controls technical section (Item 4) has been submitted to the FDA Philadelphia District Office (Maroon Binders). This copy is a true copy of Item 4 as contained in the archival and review copies of this application.

Brenda A. McGuire

Brenda A. McGuire,
M.S., R.N
Associate Director
Worldwide OTC Regulatory Affairs

11/22/02
Date



MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)

Date: September 22, 2003

From: Charles J. Ganley, M.D. _____
Director, Division of Over-the-Counter Drug Products (HFD-560)

Subject: Division Director Memo for NDA 20-325/ S-015

Recommendation

- NDA 20-325/ S-015 should be approved for relief and prevention of heartburn.
- The Directions for the prevention of heartburn can be from 10 minutes to 60 minutes before a meal.
- The labeling should include a warning statement directing consumers with kidney disease to see a doctor before using.
- The sponsor can add the "alarm symptom" warnings when other H2 blockers are requested to make those additions.
- _____ should not be permitted on the PDP unless data is provided that supports consumer understanding of what it means. There still is a prescription Pepcid product available and it is not clear what the implications are for misuse of the product with this statement on the label. We clearly do not want to encourage consumers to use this for conditions for which a prescription indication is approved.
- The graphs in the package insert are not essential to the safe use of the product and they can be eliminated if the sponsor chooses to do so.
- The sponsor should commit to conduct a phase IV clinical study in non-Caucasians to evaluate the effectiveness of Pepcid 20 mg and 10 mg for the prevention of heartburn.

Discussion

For a Pepcid 20 mg product to be marketed it should provide some benefit over the existing Pepcid 10 mg product and have a favorable risk profile. Over the past several years, the advice provided to the sponsor has evolved. Several years ago the agency held discussions with sponsors about marketing higher dosages of H2 blockers to be used for more severe episodes of heartburn. At that time, they were advised that they would have to show a significant difference between doses. Within the past year, the agency determined that emphasizing severe heartburn on a label might not be a good thing. Although there is not a direct relationship between severe symptoms and serious underlying disease, it was felt that allowing marketers to emphasize severe symptoms in labeling could encourage indefinite usage. Consumers with serious underlying conditions may continue treatment with OTC therapy indefinitely leading to a delay in diagnosis. It was also felt that requiring establishment of a statistically significant difference (pair-wise comparison) between dosages was burdensome and a significant dose response using a trend analysis for a clinically relevant endpoint would be acceptable. Many of the studies have already been conducted and were not designed to establish a dose response. Consequently, the agency has agreed to consider alternative post-hoc endpoints that are reasonable based on clinical and pharmacodynamic considerations. For Pepcid, the sponsor has provided data on stomach acidity that suggests 20 mg raises stomach pH to a greater level than 10 mg. Changes in pH alone are not an adequate surrogate for clinical benefit and additional clinical studies were needed to establish symptomatic improvement. One could hypothesize that raising the stomach pH to higher levels would result in an increase in the number of

subjects who experience symptomatic relief or it may shorten the time to relief. The burden was on the sponsor to demonstrate benefit in a clinical study.

Pepcid 20 mg is superior to placebo for relieving and preventing heartburn symptoms. This alone is not a sufficient basis to consider approval. There needs to be some evidence of an added benefit to consumers with the higher dose without a significant increase in risk. The data in the supplement supports a statistically significant difference between famotidine 20 mg and 10 mg for the pre-specified heartburn prevention endpoints. The heartburn relief studies were not adequately designed to assess a dose response.¹ There is no evidence of a dose response using the pre-specified endpoints in these studies. An alternative endpoint, the probability of complete relief in the first hour after dosing, was evaluated. It is a reasonable endpoint to consider in assessing a dose response because higher doses could shorten the time to achieve relief (in some individuals). For this endpoint, statistical significance for the comparison of 20 mg and 10 mg was not reached but there is a numerical trend supporting a dose response.

I believe the sponsor has provided sufficient evidence that 20 mg provides greater benefit than 10 mg. The significant difference in effect between dosages for the prevention endpoints was pivotal in making this decision. The numerical trend for the relief endpoint is supportive of the finding with the prevention endpoints. The indications are not mutually exclusive. Although this is not the ideal data set, there is little to be gained in having the sponsor design and conduct another study to support approval. It is more important to use resources to further evaluate the effect of therapy in non-Caucasians.

Efficacy

The sponsor provided data from three studies (study 114, 117, 128) that assessed the efficacy of famotidine 20 mg and 10 mg compared to placebo. The treatment was ingested ten minutes prior to a provocative meal. Each subject assessed the severity of heartburn over a three-hour period. The primary measure of efficacy was the peak heartburn severity measured by a four-point scale. Pepcid 20 mg was significantly better than placebo in each study for the primary endpoint. Pepcid 20 mg was significantly different from Pepcid 10 mg in Study 117 and marginally significantly different in study 114 and 128 ($p < 0.07$) for the primary endpoint. Some of the secondary endpoints supported these findings. These studies support the efficacy of famotidine 20 mg compared to placebo and a significant dose response for famotidine 20 mg compared to famotidine 10 mg. There appears to be a difference in response to therapy based on race. There was a significant treatment by race interaction for study 128 and marginally significant interaction for study 117. Caucasians appear to have greater response rates compared to non-Caucasians. Non-Caucasians were less likely to show a difference between famotidine and placebo. The sponsor should conduct additional testing in these populations as a phase IV commitment.

Two studies (study 017 and 019) were submitted to support the relief of heartburn indication. These studies were submitted previously to support the original Pepcid 10 mg OTC NDA. These were double blind, placebo controlled, multi-center, four-week treatment trials that evaluated the effect of treatment on symptomatic heartburn. Each study included groups treated with placebo, antacids, famotidine 20 mg and 10 mg. Study 017 also included a famotidine 5 mg group. Over the four week treatment period, subjects evaluated their relief from symptoms over three hours (study 017) or five hours (study 019) for each episode using a four point scale. In study 017, there is evidence of effectiveness of famotidine 20 mg and 10 mg for the primary measures of efficacy. For study 019, there was not evidence of effectiveness for the pre-specified primary efficacy measures. The longer follow-up period in study 019 compared to study 017 may have contributed to this observation. Heartburn symptoms would eventually resolve with time. The longer follow-up in study 019 lessened the ability of the study to demonstrate a difference between treatments. During the original review of Pepcid 10 mg for OTC use, study 019 was analyzed using the three-hour time frame. Based on this analysis, famotidine 20 mg and 10 mg were more effective than placebo. Because symptoms eventually resolve on their own, this analysis was reasonable and the results are consistent with those observed in study 017. The current statistical review does not support this analysis and recommends another study be conducted. From a regulatory viewpoint, it would be difficult to say that Pepcid 10 mg is effective but Pepcid 20 mg is not. The statistician has not provided a sufficient basis to reverse the decision to reanalyze study 019.

¹ In studies 017 and 019, the efficacy measures included all episodes of heartburn over a four-week period where study drug was ingested. The severity of symptoms would vary for each individual episode. Milder episodes would count the same as severe episodes. Milder episodes would be more likely to respond spontaneously, with or without therapy. This would have the effect of diluting any treatment effect and would make it difficult to demonstrate a difference between doses.

The sponsor provided a post-hoc analysis of data from study 017 and 019 to assess a dose response relationship between famotidine doses. The endpoint analyzed was the probability of complete relief one-hour after dosing using generalized estimating equations. In both studies, there is a numeric trend suggestive of a dose response. The statistical reviewer does not believe this is sufficient to support the dose response for Pepcid 20 mg. If this were the only information available, I would agree. Given that the indications are related, I believe this information is supportive of the results observed in the prevention studies.

Safety

Dr. Hu's review of safety for the Pepcid 20-mg dose recommends that the supplement not be approved. This recommendation is based on the observation that the absolute number of reported serious adverse events (SAEs) at a 40 mg total daily dose is numerically greater compared to the 20 mg daily dose. The reviewer concludes from this that there 1) is a low risk of SAEs associated with Pepcid; 2) an increased risk of SAEs with the higher dose; and 3) the risk-benefit ratio is not favorable considering the condition being treated and the availability of other therapies.

I disagree with this recommendation for the reasons outlined below.

- The post-marketing reporting for the current OTC product suggests that it is very safe. There is an enormous amount of exposure² for the OTC product throughout the world. By the reviewer's own account, the risk of a serious adverse event in the OTC setting with the 10 mg twice a day dose is extremely low. Based on this observation, even if the risk for a serious adverse event were double or tripled (which I have not seen any data to suggest), the risk for a serious adverse event is still extremely low. To believe that doubling the dose increases risk significantly, one would have to believe that this drug has a very narrow therapeutic index. There is no data to support this for Pepcid. In fact, doses up to 640 mg per day can be administered for some conditions.
- Many, if not most, of the serious adverse events reports for the prescription dosage are extremely confounded. It would be difficult to ascribe them to famotidine use. For many of the adverse event reports listed in the appendix of Dr. Hu's review, Pepcid was often prescribed for patients who were quite ill. Their subsequent demise was often attributable to preexisting conditions. Consequently, it is not reasonable to base a decision on the total number of these cases.
- The OTC product is likely to be used intermittently and in a different population of subjects compared to the prescription product. The safety data for the current OTC product is more relevant than the prescription data in assessing the risk of a higher dose. There have been _____ tablets sold OTC. If there were problems with the 10 mg twice a day dose in the OTC setting, there should be a collection of similar reports pointing to a problem. That does not seem to be the case here.
- The review notes that the available data are not adequate to determine whether a dose response exists. The review from Office of Drug Safety comes to a similar conclusion. So, the clinical trial data and the post-marketing adverse event reports do not suggest dose related serious adverse effects.
- The fact that the public has several options already available should not be taken into consideration when determining the status of this product. The OTC and prescription data suggest that the risk for a serious adverse event is extremely low.
- The exposure cannot be adequately calculated based on the available information. Consequently, the actual rate of events cannot be calculated with accuracy.

In the event the application is approved, Dr. Hu recommended ' _____
_____.³ This recommendation is based on the following:

- An initial dose reduction is recommended in subjects 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;
- The creatinine clearance in elderly decreases as a function of age;
- The elderly with health problems are likely to have a lower creatinine clearance;
- The Lin study⁴ suggests that famotidine clearance is decreased by one half in elderly (N=5, average age 69) compared to healthy young folks;

² Based on the number of pills distributed

³ _____

- Confusion is more likely to occur in subjects with impaired renal function.

After considering this recommendation, I do not concur for the following reasons:

- Longitudinal studies suggest there is a progressive linear decline in creatinine clearance related to age⁵ and subjects fall into one of three categories⁶. They can have no change, a slight increase or a progressive decline. Most people do not have significant reductions in creatinine clearance. Most do not have the level of creatinine clearance (< 50 ml/min) that triggers the recommendation for reduction in dose that is present in the current prescription label, unnecessary burden on consumers and physicians when the risk of adverse event for most consumers is quite low.
- The current prescription labeling states that there is no clinically significant age related change in pharmacokinetics and no dosage adjustment is required based on age. Physicians are not going to understand the rationale for the recommended instructions on an OTC label. They are likely to recommend using the medication twice a day. Thus, the instructions would not have the intended effect.
- The Lin study evaluated the famotidine clearance in five elderly subjects and compared it to healthy controls and to groups with decreased renal function. The clinical relevance of the decrease in famotidine clearance observed in this study is not clear. Although it is less than the healthy controls, it does not approach the decrease observed in the subjects with variable degrees of renal insufficiency. Famotidine was detected in the blood 24 hours after dosing in the groups with decreased renal function. It is somewhat reassuring that there were no detectable famotidine levels in the elderly 24 hours after dosing.
- Confusion does not appear to be a common adverse event. Aside from increased blood levels, there may be other factors that predispose subjects to it.
- Most subjects will use the OTC product on an as needed basis. The likelihood of a dose related adverse event occurring secondary to decreased elimination is more likely to occur when used daily. If there is concern about the use in elderly, it is more appropriate to consider labeling in the prescription setting where the product is used daily. It would be inappropriate to consider this labeling for the OTC setting and not in the prescription setting. Because many H2 blockers depend on renal excretion and confusion has been reported with most of them, class labeling would have to be considered. This can be discussed with HFD-180 if it is determined to be worthwhile to pursue.

Dr. Hu also recommended there be a warning for subjects with underlying kidney disease. There is a recommendation in the prescription labeling to reduce the initial dose for patients with creatinine clearance < 50 ml/min. I agree that the OTC labeling should include a warning for patients with underlying kidney disease.

Chemistry

The application is acceptable. There are no outstanding chemistry issues.

Labeling

The sponsor requested that " " be permitted on the principal display panel. Because a prescription product remains available with indications requiring diagnosis and treatment by a healthcare provider, it is unclear what this phrase will mean to consumers. The sponsor should provide data to support consumer understanding of this language on the label.

There are no other outstanding labeling issues.

⁴ Lin JH, et al. Effects of age and chronic renal failure on the urinary excretion kinetics of famotidine in man. *Eur J Clin Pharm.* 1988;34:41 - 46.

⁵ Rowe JW, et al. The effect of age on creatinine clearance in men: a cross section and longitudinal study. *J Gerontol.* 1976;31(2):155-63.

⁶ Lindeman RD, et al. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatric Society* 1985;33(4):278-85.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Charles Ganley
9/23/03 01:29:43 PM
MEDICAL OFFICER

Office Director Memo

NDA #: 20-325/S-015

Drug Name: Pepcid 20 mg

Sponsor: Merck

Type of Document: Response to Phase IV Commitment

Reviewer: Charles Ganley, M.D.

Date Completed: 6-1-06

As part of the approval of Pepcid 20 mg, Merck agreed to a phase IV commitment whereby they would conduct an efficacy study to assess the potential difference in effect in Black patients versus Caucasian patients. In lieu of the study, Merck conducted a consumer survey, reanalyzed the clinical efficacy studies in the NDA and a conducted a review of the literature.

This is what their information suggests:

- The clinical efficacy studies are suggestive of a lesser effect of famotidine in non-Caucasians but are not definitive.
- The literature does not provide any definitive information on a differential effect based on race. There was a lack of data to review rather than data suggesting no difference.
- Through a freedom of information request, they provide some information that other H2 receptor antagonist (e.g. nizatidine) may have lesser efficacy in black.
- The consumer survey suggests that similar percentages of Black and Caucasian users of famotidine find it to be effective. This survey can not be used to demonstrate efficacy. It is somewhat biased in that it included consumers who used H2 receptor antagonists. It is not clear how they were recruited but it may have selectively excluded consumers who did not find it effective.

Conclusion

The information submitted does not readily address the phase IV request. However, it is evident from the consumer survey that some Black consumers find Pepcid to be an effective therapy. Given the way the OTC market functions, consumers will select and continue to use medicine based on how it works for them. For H2 blockers, they will not be effective for all consumers and those who do not find them helpful will no longer purchase them. So, even if we were able to demonstrate a differential effect in populations based on race, it is unlikely it would lead to a change in labeling. The only data that would be of consequence would be a demonstration that the drug is not effective at all in a sub-population. Merck's survey, in some respects, suggests that there are Black consumers who find it to be an effective therapy. So, I believe there is little benefit to have them conduct an efficacy study at this time.

Recommendation

Merck should be released from their commitment to conduct an efficacy study at this time.

Charles J. Ganley, M.D.
Director, Office of Nonprescription Products

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Charles Ganley
6/2/2006 12:41:04 PM
MEDICAL OFFICER

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 7, 2004

FROM: Lolita A. Lopez, M.D.
Medical Officer
Division of Gastrointestinal and Coagulation Drug Products,
HFD-180

TO: Charles Ganley, M.D.
Director
Division of Over the Counter Drug Products, HFD-560

THROUGH: Ruyi He, M.D.
Medical Team Leader, GI Team II
Division of Gastrointestinal and Coagulation Drug Products,
HFD-180

AND Joyce Korvick, M.D., M.P.H
Deputy Director
Division of Gastrointestinal and Coagulation Drug Products,
HFD-180

SUBJECT: Consultation from HFD-560

NDA: 20-325/S-015

Type of Document: Phase IV Efficacy Data

Sponsor: Merck & Co., Inc.
BLX-29, P.O. Box 4
West Point, PA 19486

Drug Name: Famotidine (Pepcid AC) Oral Tablet 20mg

Indication: Prevention and Treatment of Intermittent Heartburn

I. BACKGROUND

Pepcid (famotidine) is an H₂-receptor antagonist (H₂RA) which has been approved in the United States since October, 1986 for the treatment of a variety of acid-related gastrointestinal disorders. This drug binds to the parietal cell H₂-receptor and competitively inhibits histamine-stimulated gastric acid secretion, thereby raising intragastric pH. It is currently available by prescription as 20-mg and 40-mg tablets, orally disintegrating tablets; oral suspension (40 mg/5 mL); and parenteral formulations. On April 30, 1995, Pepcid® AC 10 mg became available for OTC use. Pepcid® AC 20 mg became available for OTC use in September, 2003.

Pepcid AC 20 mg was submitted under NDA 20-325, S-015 and was approved on September 23, 2003 for the prevention and treatment of episodic heartburn for OTC use. The approval included a Phase IV sponsor commitment to conduct a clinical trial to assess the efficacy of famotidine 10-mg and 20-mg for the prevention of heartburn in non-Caucasians after a provocative meal. The Agency was concerned over the clinical data suggesting that non-Caucasians (primarily African Americans) experienced less efficacy from the drug in the prevention of heartburn compared to Caucasians.

II. THE PURPOSE OF CONSULTATION

As a response to the Phase IV commitment, the sponsor has submitted efficacy data from mined clinical databases, published literature, Freedom of Information (FOI) and consumer research study to the Division of Over-the-Counter Drug Products (OTC). These were done in place of submitting a proposed efficacy study for famotidine 10-mg and 20-mg in the non-Caucasian population following a provocative meal as agreed upon at the time of approval. The sponsor concluded that these data support that famotidine use in the non-Caucasian population is effective and requests that this response document be considered as evidence of their attempt to address the treatment-by-race interaction issue and be released from the commitment to conduct a clinical trial.

The Division of OTC is requesting this Division (GI and Coagulation Drug Products) to briefly review the content of this submission and determine if the sponsor has submitted enough data to evaluate the efficacy of famotidine in the non-Caucasian population following a provocative meal.

III. COMMENTS

A. Consumer Research Study

The sponsor conducted a consumer research study to determine whether a difference exists between Caucasians and African Americans in perceived efficacy of Pepcid® OTC (famotidine) when used for *preventing* heartburn or indigestion.

This report primarily focuses on the key issue of *efficacy perception* between the subgroups who have used Pepcid® OTC. This was conducted in malls at 27 locations dispersed across the United States and each site recruited equal numbers of African Americans and Caucasians 18 years of age or older, who have used a H₂RA (famotidine, ranitidine, cimetidine or nizatidine) to prevent heartburn or indigestion.

Participants included 388 Pepcid® prevention users (196 African American and 192 Caucasians), and 97 “Other” H₂RA users (41 African Americans and 56 Caucasians). The sample groups were balanced with regards to age, gender, income; and included both current and “lapsed” Pepcid® users. The “lapsed” users were those who may have used Pepcid® in the past but not currently using it.

The results of the study showed that more African Americans who had used Pepcid® OTC for prevention were current users compared to Caucasians (84% versus 76%). Among the total Pepcid® OTC sample (current + lapsed), there is no perceived efficacy difference for Pepcid® used to prevent stomach problems (e.g. heartburn or indigestion) between the two groups. Seventy seven percent (77%) of African Americans and 73% of Caucasians indicated that Pepcid® is extremely or very effective.

Regardless of race, approximately two-thirds of consumers (62% African Americans; 66% Caucasians) agree that the product works every time they take it. A higher proportion of African Americans compared to Caucasians (58% vs. 43%) said that Pepcid® AC “costs more but is worth it”. In addition, there were no significant differences between the two racial subgroups with regards to attitudes about Pepcid® OTC, profile from suffering and treating of stomach problems.

A consumer research study should not be regarded as pivotal in evaluating the difference in efficacy of famotidine between racial groups. However, the clinical outcome for GERD is measured mainly by self-report of symptoms; therefore, the consumer research study conducted by the sponsor provides a reasonable supporting information. This study indicated that there is no difference between African Americans and Caucasians in the perceived efficacy of Pepcid in the prevention and treatment of heartburn.

B. Supplemental NDA Clinical Studies (NDA 20-325/S-015)

Three prevention studies (Protocols 114, 118 and 128) and two treatment studies (Protocols 017 and 019) were included in this submission (NDA 20-325/S-015). A total of 3,357 patients participated in the three prevention studies: 75.8% (2,547) were Caucasians and 24.1% (810) were non-Caucasians. Of the non-Caucasians, 611 were African Americans, comprising 18.2% of the total population who participated in the prevention studies.

An analysis for treatment-by-race interaction was performed and results showed that in *one* of the *prevention* studies (P128) there was a significant statistical interaction by

race; P117 was marginal; and P114 showed no treatment-by-race interaction. No treatment by race interaction was noted in the acute heartburn *treatment* studies (P017 & 019). No definite explanation was found to account for the difference in the response between these racial subgroups.

One possible explanation is that none of the prevention studies in the application were statistically powered to show a difference among racial subgroups. The statistical analysis plans in the protocol were powered to detect a difference between the two dosage strengths of famotidine, i.e. 10 and 20 mg; and between active control and placebo.

C. Published Literature

A published literature search on H₂RAs class focusing on the response of non-Caucasians to H₂RAs and proton-pump-inhibitors (PPIs). No information was found to support a racial difference in H₂RA efficacy in the *prevention* of heartburn.

The literature also addresses the racial disparities in enrollment of non-Caucasians into clinical studies. In many clinical studies, a relatively small number of non-Caucasians participants as compared to Caucasians limit the ability to establish a precise estimate of the subpopulations' response to treatment.

IV. SUMMARY

Supplemental NDA data (3 prevention studies and 2 treatment studies) have demonstrated only one study with a statistically significant treatment-by-race interaction. This study was not statistically powered to show a difference among racial subgroups in the prevention of heartburn. Published literature did not support the difference in efficacy between the racial groups. The consumer research study conducted by the sponsor is supportive of the efficacy of Pepcid in the prevention of heartburn by both racial subgroups.

The sponsor had investigated and analyzed the treatment-by-race interaction issue in the prevention of heartburn. Pepcid was approved for use in the USA for almost 18 years now and continues to be prescribed by physicians for its listed indications. It has been proven in the clinical setting that this medication is effective and no concerns has so far been raised with regard to the difference in its efficacy among racial subgroups in the prevention and treatment of heartburn.

V. CONCLUSION

Based on current available data, there is no strong evidence indicating that a significant difference exists between African Americans and Caucasians in the efficacy of famotidine for the prevention and treatment of heartburn. The sponsor has provided a reasonable data on the efficacy of famotidine in the non-Caucasian (primarily African American) population. Therefore, I consider this submission the fulfillment of the

sponsor's post-marketing commitment to assess the efficacy of famotidine for the prevention of heartburn in non-Caucasians after a provocative meal.

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Lolita Lopez
5/11/04 11:28:16 AM
MEDICAL OFFICER

Ruyi He
5/11/04 05:56:12 PM
MEDICAL OFFICER

Joyce Korvick
5/12/04 10:16:00 AM
MEDICAL OFFICER
for Dr. Robert Justice

-----Original Message-----

From: Shay, Laura [mailto:ShayL@cder.fda.gov]
Sent: Monday, September 22, 2003 1:38 PM
To: 'brenda_mcguire@merck.com'
Cc: Hilfiker, David R
Subject: Phase IV commitment

Hi Brenda, this is basically the outline of what is required when defining a Phase IV commitment. If you and your team could draft a proposal for a clinical trial to assess the efficacy of famotidine 10mg and 20 mg for the prevention of heartburn in non-Caucasians subjects after a provocative meal by 3:00 PM today we can work on coming to an agreement on your final proposal. Thank you.

Description of Commitment:

Protocol Submission:	Within X months
Study Start:	Within Y months
Final Report Submission:	Within Z months

Laura E. Shay, MS, RN, C-ANP
Regulatory Project Manager
Division of Over-The-Counter Drug Products HFD-560
Centers for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-827-2274
Email: ShayL@cder.fda.gov

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Laura Shay
10/24/03 12:59:58 PM
UNKNOWN

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 31, 2003

FROM: Lauren Lee, Pharm.D., Safety Evaluator
Cynthia Kornegay, Ph.D., Epidemiologist
Division of Drug Risk Evaluation, HFD-430

THROUGH: Mark Avigan, M.D., Acting Director
Division of Drug Risk Evaluation, HFD-430

TO: Charles Ganley, M.D., Director
Division of Over-The-Counter Drug Products, HFD-560

SUBJECT: ODS Post-Marketing Safety Review (PID# D030375)
> Drug: Pepcid (famotidine tablets); NDA 20-325
> Reaction: Serious hematological adverse events

Confidential: Contains IMS data; not to be used outside of the FDA without clearance from IMS.

I. EXECUTIVE SUMMARY:

This consult is in response to a request, by the Division of Over-The-Counter (OTC) Drug Products, to review AERS case reports of serious hematological adverse events in association with oral famotidine tablets and to compare the occurrence of these events for 20 mg versus 40 mg total daily doses. Famotidine is available as both prescription-only (Rx) {20 mg, 40 mg} and OTC {10 mg} tablets. The Rx indications include short-term treatment of duodenal ulcer, active benign gastric ulcer, gastroesophageal reflux disease, and pathological hypersecretory conditions, and maintenance therapy for duodenal ulcer. The OTC indication is for relief and prevention of heartburn.

The AERS database was searched for adverse event reports received since drug approval (October 15, 1986) to December 31, 1994 (prior to Rx-to-OTC switch) in order to exclude cases that were related to OTC use, primarily because OTC products differ from Rx products in that there is different drug labeling and access to patients (that can affect the reporting of adverse events). The searches revealed 37 cases, of which 34 reported the following adverse events: pancytopenia (12), thrombocytopenia (12), leukopenia/neutropenia (5), aplastic anemia (2), agranulocytosis (2), and unspecified bone marrow depression (1). The remaining three cases reported both thrombocytopenia and leukopenia/neutropenia. Seventy percent (70%) of the events occurred in patients taking 40 mg per day and 11% taking 20 mg per day. However, the numbers are small for the groupings and notable differences in the demographic data, underlying medical history, and the types of hematological reactions were not observed between the 20 and 40 mg groups. Outcomes included 16 deaths (43%) and 20 hospitalizations (54%). Nine of 16 deaths occurred in the 40 mg group, 3 deaths in the 10-20 mg group, and 4 deaths in the dosage unknown group. In 6 of 16 cases, the reporter stated that the fatal outcome was possibly related to famotidine use [20 mg (1), 40 mg (3), dosage unknown (2)].

An analysis using the available IMS Health drug utilization databases was limited and did not provide and helpful information regarding a possible drug effect.

Conclusion

The AERS data indicate that more cases of serious hematological adverse events and deaths were reported with the use of famotidine 40 mg tablets compared to 20 mg tablets in the post-marketing setting. However, these findings do not provide evidence of a dose effect in relation to drug adverse events and outcomes since the AERS database is not designed to quantitatively measure risks associated with these events. Clinical study databases may be a better source to determine a dose effect.

II. DRUG INFORMATION AND US LABELING:

The drug applicant (Merck) has proposed to switch famotidine 20 mg tablets from Rx to OTC status (*maximum daily dose: 40 mg*) for the prevention and treatment of heartburn. Famotidine 10mg tablets have been available for OTC use since April 1995 (*maximum daily dose: 20mg*). If the sponsor's proposed strength (20 mg) is approved for OTC use, a total daily dose of 40 mg can be ingested using either Rx or OTC tablet strengths.

Table 1. Drug information

Drug Product	NDA	Applicant	FDA Approval	Approved Strengths
Pepcid (famotidine tablet) - Rx	19-462	Merck	10/15/86	20 mg, 40 mg
Pepcid (famotidine injection) - Rx	19-510	Merck	11/4/86	10 mg/mL
Pepcid (famotidine injection) (preservative free) - Rx	19-510	Merck	11/4/86	10 mg/mL
Pepcid (famotidine oral suspension) - Rx	19-527	Merck	2/2/87	40 mg/5 mL
Pepcid (famotidine injection) (preservative free in plastic container) - Rx	20-249	Merck	2/18/94	0.4 mg/mL
Pepcid AC (famotidine tablet) - OTC	20-325	Merck	4/28/95	10 mg
Pepcid AC (famotidine chewable tablet) - OTC	20-801	Merck	9/24/98	10 mg
Pepcid Complete (famotidine; calcium carbonate, precipitated; magnesium hydroxide) chewable tablet - OTC	20-958	Merck	10/16/00	10mg; 800 mg; 165 mg

❖ Rx - Package Insert Labeling (Revised version approved by FDA in March 2001)

Adverse Reactions

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

❖ OTC Labeling - Hematologic events are not labeled.

III. SELECTION OF CASE SERIES:

As of 7/1/03, AERS contained a total of 10,156 adverse event reports in association with famotidine. Additional AERS searches were conducted using the following criteria to identify serious hematological adverse events in association famotidine.

Table 2. AERS Search Criteria

Drug Names	MedDra Search Terms	Selected Outcomes	Crude Counts	Receipt Dates
<ul style="list-style-type: none">• Pepcid• Famotidine	<ul style="list-style-type: none">• Agranulocytosis (preferred term [PT])• Aplastic anaemia (PT)• Bone marrow depression (PT)• Granulocytopenia (PT)• Leukopenia NOS (PT)• Neutropenia (PT)• Pancytopenia (PT)• Thrombocytopenia (PT)	<ul style="list-style-type: none">• Congenital anomaly• Death• Disability• Hospitalization• Life-threatening	120	*From: approval To: 12/31/94

*This time interval was selected to exclude adverse event reports from OTC use.

Eighty-three (83) of 120 AERS reports were excluded from further analysis based on the following:

Table 3. Exclusions

Adverse event reports involving intravenous famotidine	60
Adverse events likely related to underlying medical conditions or other drugs	17
Duplicates	4
Adverse event reports not readable	2
Total	83

The remaining 37 cases were included in this case series.

IV. SUMMARY OF CASES:

Table 4. Demographic Data of Serious Hematologic Events (N=37)

Total Daily Dose:		[All:40,20,&10 mg] (N=37)	40 mg (N=26)	20 mg (N=4)	10 mg (N=1)	Dose Unknown (N=6)
Age (yrs):	Range	15-87 (N=34)	15-87 (N=26)	39-80 (N=3)	N/A: [76 yrs]	44-77 (N=4)
	Median	66	65	66		70
Gender:	Male	12	10	1	0	1
	Female	24	16	3	1	4
	Not stated	1	0	0	0	1
Indications:	Ulcer (incl prophylaxis for ulcer)	10	7	1	1	1
	Gastritis	6	6	0	0	0
	Abdominal pain	6	5	1	0	0
	Esophagitis	3	2	1	0	0
	GI hemorrhage	3	2	0	0	1
	Not stated	9	4	1	0	4
Estimated time to onset:	Range	3-103 days (N=27)	3-90 days (N=21)	6-103 days (N=4)	N/A: [6 days]	N/A: [11 days (N=1)]
	Median	16 days	17 days	19 days		
Diagnosis:	Pancytopenia	12	9	1	1	1
	Thrombocytopenia	12	9	2	0	1
	Leukopenia/neutropenia	5	3	0	0	2
	Thrombocyto + leuko/neutropenia	3	3	0	0	0
	Aplastic anemia	2	0	1	0	1
	Agranulocytosis	2	1	0	0	1
	Unspecified bone marrow depression	1	1	0	0	0
Outcomes:	Death	16	9	2	1	4
	Hospitalization (HO)	18	16	2	0	0
	HO + RI* + LT**	1	1	0	0	0
	HO + DIS + LT	1	0	0	0	1
	Other	1	0	0	0	1
Drug dechallenge/ rechallenge:	Positive Dechallenge	14	13	1	0	0
	Negative Dechallenge	9	5	2	1	1
	Positive rechallenge	1	1	0	0	0
	Not stated	13	7	1	0	5
Location:	US	20	16	2	0	2
	Foreign	17	10	2	1	4
Report type:	15-day	24	17	2	1	4
	Periodic	7	6	1	0	0
	Direct	6	3	1	0	2

*RI = required intervention; **LT = life-threatening

Seventy percent (70%) of the above events occurred in patients taking 40 mg per day and 11% taking 20 mg per day. However, the numbers are small for the groupings and notable differences in the demographic data, underlying medical history, and the types of hematological reactions were not observed between the 20 and 40 mg groups. Overall, the patients were mostly older (median age 66 years) and female (24/37). Famotidine was prescribed most often for prophylaxis or treatment of ulcer. The median time of onset was 16 days. Forty-six percent of the reports were received from foreign sources.

Outcomes included 16 deaths (43%) and 20 hospitalizations (54%). Nine of 16 deaths occurred in the 40 mg group, 3 deaths in the 10-20 mg group, and 4 deaths in the dosage unknown group. In 6 of 16 cases, the reporter stated that the fatal outcome was possibly related to aplastic anemia (2), leukopenia (2), agranulocytosis (1), and pancytopenia (1). In 4 of these 6 cases, disseminated intravascular coagulation, pancreatic carcinoma, multi-organ failure/pneumonia, SLE, respectively, were also contributing factors of the outcome. The reported causes of death in the remaining 10 cases were bleeding/hemorrhage (2), respiratory failure (1), cardiorespiratory arrest (1), cardiac and renal failure (1), possible sepsis/shock/cardiac arrest (1), pneumonia (1), sudden death (1), unrelated causes (1), and not available (1). Four of these 10 patients had an underlying history of heart failure, cardiomyopathy, respiratory failure, renal failure, pulmonary edema, and/or polytrauma that probably contributed to the fatal outcome.

Available laboratory values were consistent with the reported events in 31 cases, but many did not report blood counts for all three cell lines. In 9 cases, baseline values were stable or within the normal range prior to famotidine administration. Since various laboratory parameters were used in foreign countries, the laboratory findings of only the US cases are outlined below:

Table 5. Laboratory Findings

Adverse Events for US Cases	Laboratory Findings
Thrombocytopenia	PLT: 2,000-82,000/ μ l (N=10)
Pancytopenia	WBC: <1000-1400/ mm^3 (N=2) PLT: 60,000/ μ l (N=1) Hgb: 7 gm/dL(N=1)
Leukopenia/neutropenia	ANC: 300 (N=1) WBC: 500-2200/ mm^3 (N=2)
Leukopenia/neutropenia and thrombocytopenia	PLT: 12,000/ μ l (N=1)

The results of the bone marrow biopsies/aspirates were available in 6 of 37 cases, but only 2 cases specifically mentioned a drug-association. Eighteen cases were confounded by the use of concomitant medications that are labeled with the reported hematological events. Five patients had concomitant sepsis or pneumonia (unknown if preceded heme events) and 2 patients had liver abnormalities. Significant medical history included renal failure (3), liver dysfunction (4), liver transplant (1), and SLE (1), which could have contributed to the susceptibility of the reported adverse events. Two patients had a history of leukopenia and/or thrombocytopenia, but the most recent occurrence of these events was temporal to famotidine administration.

V. EPIDEMIOLOGICAL ASSESSMENT:

National Prescription Audit Plus

Description

IMS Health's National Prescription Audit Plus (NPA) measures the retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. These retail pharmacies include chain, independent, food store, mail order, discount houses, and mass merchandiser pharmacies, as well as nursing home (long-term care) pharmacy providers. The number of dispensed prescriptions is obtained from a sample of approximately 22,000 pharmacies

throughout the U.S. and projected nationally. The pharmacies in the database account for approximately 40% of all pharmacy stores and represent approximately 45% of prescription coverage in the U.S.

Analysis

For all product strengths, total prescriptions were obtained for the calendar years 1987 through 1994. Only oral solid products were included (e.g., tablets, gelcaps, caplets, etc.). For the years 1987 through 1997, information was from hardcopy books. In cases where the book totals were adjusted (i.e., total Rx's for 1988 were higher in the 1989 book than in the 1988 book), the higher number was used, since it was based on more complete information.

Limitations

NPA data provides a projected estimate of the total number of prescriptions dispensed in the U.S. for a particular product. However, it does not include demographic information for the patients receiving these prescriptions, such as age and gender. Since only prescription data are recorded it is not possible to estimate or derive the number of people who received the drug. In addition, no information on quantity dispensed or instructions for use is provided in the hardcopy books, so it is not possible to estimate an average daily dose.

National Sales Audit

Description

IMS Health's National Sales Audit (NSA) enumerates what was sold to hospitals and retail pharmacies nationwide. This audit provides national sales estimates of drugs purchased by retail drugstores, mail-order pharmacies, and non-retail outlets (e.g., non-federal and federal hospitals, long-term care, prisons, etc.) All branded and generic drugs are represented, with coverage estimated at 100% of prescription drugs and 50% of the over-the-counter drugs sold to these facilities in the U.S.

The NSA measures include the amount of drug sold, or unit, and the cost of the drug. Units can be further broken down into "extended units" or "eaches", based on the form of the drug. "Extended units" are defined as a single tablet. For non-solid drugs (e.g., liquid, cream, aerosol), "eaches" are defined as a single dose of the drug. The number of "extended units" or "eaches" sold is calculated by multiplying the number of units sold by the package size of the drug.

Analysis

Data for combined hospital and retail sales for 1986 through 1994 were obtained from hardcopy books. Only oral solid products were included (e.g., tablets, gelcaps, caplets, etc.). Extended units were calculated by multiplying the package size (i.e., bottle size, number of blister packs) by the number of units sold for each available product strength.

Limitations

The NSA measures the number of individual pills sold, so it is not known how many people are exposed based on this measure. Also, there is no link between these data and what was used by patients, so no individual dosage information can be obtained. The NSA for this period of time does not include drugs sold to all sources (e.g., samples, long-term care, mail-order), but these sources may not be significant for the time period in question.

National Disease and Therapeutic Index

Description

The National Disease And Therapeutic Index (NDTI) is a continuing survey designed and conducted by IMS Health to provide descriptive information on the patterns and treatment of disease encountered in office-based practice in the continental United States. NDTI collects data on drug products mentioned during visits to office-based physicians in the U.S. The data are gathered by a panel of roughly 2000 to 3000 office-based

physicians in the continental U.S. For two consecutive days per quarter, the physicians complete and submit a survey of their practice patterns to IMS Health. These data may include profiles and trends of diagnoses, patients, and treatment patterns. The data are collected and projected to the national level to obtain an estimate of use.

NDTI uses the term "appearances" and "uses" for drug reports. A drug appearance roughly translates to a mention of a drug during a patient visit, unduplicated by the number of diagnoses for which it may be used. A drug appearance can result from a prescription written, a refill authorized, a sample given, the drug administered in the office, etc., or any combination of these. For example, a patient receiving a sample of a drug and also a prescription for that same drug for two different indications will be counted as one drug "appearance." On the other hand, NDTI also uses the term "uses" for mentions of a drug in association with a diagnosis during a patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. Due to the differences in definitions for these measures, the counts may vary slightly from one another for the same attribute, such as gender or age. However, the differences observed between these measures are not likely to be substantial.

Analysis

Projected appearances were calculated for each total daily dose (TDD) from April 1987 through December, 1994. Only oral solid products were included (e.g., tablets, gelcaps, caplets, etc.). Product, product strength, and instruction information were extracted from the CD's, and TDD was estimated based on the product strength and instructions. Instructions of "less than one" were assumed to mean ½ pill. Instructions of "one every 1 hour" were calculated based on a 16-hour day (i.e., 16 pills per day). Instructions of one every 4, 6, or 8 hours were calculated based on a 24-hour day (i.e., 6, 4, and 3 pills per day, respectively). Cases where either the strength or instructions were unknown, or in cases where a TDD could not be calculated (e.g., "tapering dose", "1 every three weeks", "1 time only"), were put into the Unknown category.

Limitations

Data are collected at the physicians' office, and thus may reflect intent of the physician but not the behavior of the patient. The sample numbers, from NDTI can be very small and unreliable. This may result in projected estimates that are unstable. The numbers do not generally reflect actual prescriptions, as an "appearance" may include hospital orders written, samples given, or a discussion with no action taken, etc. in addition to prescribing. NDTI is not designed to represent all office-based physicians or all patient office visits, and estimates obtained using NDTI may not be representative of all populations of interest. It is not known how well the NDTI patient population represents the U.S. Depending on the product in question, there may be a significant amount of missing information for key variables. (For famotidine, approximately 38% of the appearances were missing strength and/or instruction data for the years in question.) The population included in this audit cannot be described in epidemiologic terms. Basic sampling information (e.g., number of physicians, number of visits, etc.) necessary to place the data in context are proprietary to IMS Health, and has not been shared with the FDA.

Analysis of Domestic Adverse Events

For the period of 1987 to 1994, graphs were created that plotted the number of domestic adverse event reports (domestic AE's) and domestic AE mortality against total prescriptions (NPA), extended units (NSA), and drug appearances (NDTI). Briefly, NPA provides a projected estimate of the number of prescriptions for both the 20 mg and 40 mg strengths of famotidine. The NSA enumerates the number of pills sold to pharmacies and hospitals for each strength, and NDTI supplies projected estimates of the range of recommended daily doses of famotidine. All denominator values are for the tablet forms of famotidine only.

Domestic AE's vs. NPA (See Appendix graph 1 & 2)

At the 20 mg strength, there were 2 domestic AE's and an estimated _____ prescriptions between the years of 1987 and 1994. For the estimated _____ 40 mg prescriptions, there were 16 domestic AE's for the same time period. Although there were more adverse events reported at the 40 mg level, it is not known how the drugs were prescribed – i.e., if the prescription was for two 20 mg tablets or a single 40 mg dose. The same pattern was seen when only domestic AE deaths were examined. In addition, it is not known how many individuals are represented by the number of prescriptions. Although it does appear that the chance of a reported domestic AE increases with the strength of the product, these limitations prevent a valid direct comparison.

Domestic AE's vs. NSA (See Appendix graph 3 & 4)

For the NSA, there were an estimated _____ 20 mg pills and _____ 40 mg pills sold during the time period of interest. Since the NSA tallies only what was sold, it is not known if or how these drugs were used by patients. Similar to the NPA graph, there appears to be a greater chance of a reported domestic AE and a domestic AE death with the higher strength of famotidine.

Domestic AE's vs. NDTI (See Appendix graph 5 & 6)

The count of reported domestic AE's was plotted against the projected total daily dose (TDD) for famotidine for 1987 through 1994. The same adverse event trend seen in the NPA *Plus* and NSA graphs is seen here as well, although the large amount of missing dose data (approximately 40%) could affect the validity of the result. In addition, while there were TDD's in the range of 5-10 mg and 80 mg and above, all of the reported domestic AE's were for either 20 mg, 40 mg or an unknown dose. If there was a chance of a dose-related increase of an adverse event, an adverse event at extremely high doses (range of 80 mg to 360 mg per day) would not be unexpected. However, the number of individuals in this range of TDD's may be quite small. The sample numbers used to obtain projected values for NDTI may be quite small, and therefore both the sample and projected values could be widely variable and statistically unstable.

Discussion of Epidemiology Analysis

While an appropriate denominator group was not available for comparison in this analysis, three databases from IMS Health were used as proxy denominators. For domestic AE's, all three graphs showed an increased chance of either a reported event or a death at the 40 mg dose versus the 20 mg dose. The NPA *Plus* and NSA graphs show a lower utilization of the 40 mg dose with this higher AE reporting, but given the lack of information about actual dose consumed (not sold), no conclusion about risk can be made. For the graph that compared the domestic AE's to NDTI, there were no adverse events above the 40 mg daily dose, although some of the calculated doses ranged up to 360 mg per day. This could be due to the relatively small number of individuals who were taking very large doses of famotidine during this time period. Thus the limitations of using available drug sales/mentions data indicate that no clear conclusions can be made regarding a possible dose effect.

VI. OVERALL CONCLUSION:

The AERS data indicate that more cases of serious hematological adverse events and deaths were reported with the use of famotidine 40 mg tablets compared to 20 mg tablets in the post-marketing setting. However, these findings do not provide evidence of a dose effect in relation to drug adverse events and outcomes since the AERS database is not designed to quantitatively measure risks associated with these events. Clinical study databases may be a better source to determine a dose effect.

Signed 07-31-03

Lauren Lee, Pharm.D.
Safety Evaluator

Signed 08-01-03

Cynthia Kornegay, Ph.D.
Epidemiologist

Concur:

Signed 08-01-03

Claudia Karwoski, Pharm.D.
Safety Evaluator Team Leader

Signed 08-01-03

Mary Willy, Ph.D.
Epidemiology Team Leader

Redacted 6

7/31/03
Post-marketing safety review
consult, Attached Appendices

Page(s) of trade

secret and /or

confidential

commercial

information

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Lauren Lee
8/1/03 11:35:45 AM
PHARMACIST

Mark Avigan
8/1/03 05:27:50 PM
MEDICAL OFFICER



T-Con Memorandum

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)

Date: July 17, 2003

From: Charles J. Ganley, M.D. _____
Director, Division of Over-the-Counter Drug Products (HFD-560)

Subject: NDA 20-325/S-015, Extra Strength Pepcid 20 mg
Merck, Johnson & Johnson

Participants: Charles Ganley, M.D.
Ed Hemwall, Ph.D.
Brenda McGuire
Jeff Levine, M.D.

Background

The sponsor received labeling comments on July 14, 2003 for the Extra Strength Pepcid 20 mg. The reviews are not completed yet and the regulatory action has not been decided. There were several parts of the label that they wanted to discuss. They hope to agree on labeling so that if the application were approved they would be able to get the product on the shelves of stores this fall. If they are unable to come to closure on labeling, they will not be able to market the product until next year.

Issues:

1. "kidney problems"
 - Consumers are likely to lump in many other conditions related to the bladder (e.g. UTI) when the word "problems" is used. Exact language such as "disease" is better.
 - They would like to use the warning used for antacids. "Do not use if you have kidney disease _____ supervision of a _____."

Response:

They can use the warning that is currently in the monograph for antacids.

2. " _____ "
 - They believe that the occurrences of these events are rare and mention of them in the label is not warranted. The Rx labeling is full of reported adverse events, not just this one, and it is not clear why this one should be included.
 - Many of the events are associated with people who had severe or moderate kidney disease or had received intravenous famotidine.

Response:

I have not seen an internal review that discusses this issue. They have included a summary of these adverse events in their submission that describes the data. If the data is as they describe it, then it may not be an applicable warning for an OTC product.

3. Alarm symptoms
 - They would like to include the alarm symptoms when all of the other H2 blockers are asked to do it.

Response:

It is acceptable to include the alarm symptoms when all of the H2 blockers are asked to do it.

Action Items:

1. Merck will submit comments on the labeling. They should include a brief discussion of the issues related to the _____ warning and describe why they do not believe it is warranted.

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Charles Ganley
7/17/03 08:52:45 AM
MEDICAL OFFICER



MEMORANDUM of T-Con

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)

Date: 7-2-03

From: Charles J. Ganley, M.D. _____
Director, Division of Over-the-Counter Drug Products (HFD-560)

Subject: T-con with Dr. Ed Hemwall at Merck regarding Maximum Strength
Pepcid AC 20 mg labeling

To: NDA 20-325/S-015

Background

Merck wants to pre-print labels for their proposed 20 mg Pepcid product at their own risk. They would use the exact language in the Pepcid AC 10 mg product with the exception of the substitution of the different name and dosage strength. The graphs in the package insert would also include data relevant to 20 mg.

T-Con

- The reviews of the application are not complete and so it has not been determined whether we view the product to be safe and effective for OTC use. There are still issues to be resolved for both efficacy and safety.
- For them to be assured that we would have no problem with the pre-printed label, they can do the following.
 - Use the language in the 10 mg Pepcid as noted above.
 - Add a kidney warning under the Ask a doctor before use section.
 - Add a _____ warning under the Stop use and ask a doctor section
 - Do not put " _____ " on the PDP
 - Take out the graphs on the package insert.
- If they do not include a renal warning or _____ warning, they are taking an increased risk that the pre-printed label would not be acceptable.
- After further discussion, Dr. Hemwall stated that they would not proceed with pre-printing but would like to have comments as soon as possible on the label that they sent to us in the submission.
- I told him that we will try to get him comments by sometime early next week.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Charles Ganley
7/2/03 02:14:10 PM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: June 23, 2003

APPLICATION NUMBER: NDA 20-325, Pepcid AC (famotidine)

BETWEEN:

Name: Brenda A. McGuire, OTC Regulatory Affairs
Dr. Ed Hemwall, OTC Regulatory Affairs
Dr. Sanford Smith, Worldwide Product Safety and Epidemiology
Dr. Jeff Levine, OTC Clinical Research
Phone: 484-344-7235
Representing: Merck

AND Division of Over-the-Counter Drug Products, HFD-560
Name: Laura Shay, Regulatory Project Manager
Linda Hu, M.D., Medical Officer
Andrea Leonard Segal, Medical Team Leader

SUBJECT: Data Request

This T-con was requested by Merck in response to the facsimile sent to them on June 19, 2003, requesting additional safety data pertaining to hematologic adverse events (AEs). The following is a summary of the discussion.

The Agency requests from the Sponsor's "Japan" and "Total World Wide" data base, the subsets of hematologic AEs by oral dose, the number of deaths due to hematologic AEs, and the number of AE's with more than one reported hematologic event. In addition the Agency requested, to the best of the Sponsor's ability, a calculation per person years with the understanding that this data may be based on a denominator with assumptions derived from the number of tablets dispensed and/or the number of prescriptions. An absolute denominator is not available. Re-challenge information was also requested but is not available. the Sponsor agreed to obtain this information as quickly as possible.

Laura Shay
Regulatory Project Manager

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Laura Shay
6/24/03 12:28:48 PM
UNKNOWN

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 12/19/02

DUE DATE: 3/31/03

ODS CONSULT #: 02-0224

TO:

Charles Ganley, M.D.
Director, Division of OTC Drug Products
HFD-560

THROUGH:

Dan Keravich
Project Manager, Division of OTC Drug Products
HFD-560

PRODUCT NAME:

Pepcid AC Maximum Strength (Famotidine Tablets)
20 mg

NDA #: 20-325/S-15

NDA SPONSOR: Merck

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of OTC Drug Products (HFD-560), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Pepcid AC Maximum Strength" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:

1. DMETS has no objection to the use of the proprietary name "Pepcid AC Maximum Strength".
2. DDMAC finds the proprietary name, "Pepcid AC Maximum Strength", acceptable from a promotional perspective.
3. DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA supplement. A re-review of the name prior to NDA supplement approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

Carol Holquist, R.Ph.
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 25, 2003

NDA NUMBER: 20-325/S-15

NAME OF DRUG: Pepcid AC Maximum Strength (Famotidine Tablets) 20 mg

NDA HOLDER: Merck

I. INTRODUCTION:

This consult was written in response to a request from the Division of OTC Drug Products (HFD-560) for assessment of the proprietary name "Pepcid AC Maximum Strength" regarding potential name confusion with other proprietary/established drug names. The name, "Pepcid AC", for famotidine 10 mg has been in use in the OTC market since April 28, 1995. The sponsor now proposes a famotidine 20 mg tablet to be introduced into the OTC market. To avoid confusion, the sponsor proposes the phrase "Maximum Strength" to be used in conjunction to the already existing name "Pepcid AC" for the 20 mg tablet. DMETS also reviewed the package insert pouch that was submitted. Container labels and carton labeling were not submitted to DMETS.

PRODUCT INFORMATION

"Pepcid AC" is the proprietary name for the OTC product famotidine. Famotidine is a histamine H₂-receptor antagonist. It is indicated for the relief or prevention of the symptoms of heartburn, acid indigestion, and sour stomach. In the OTC market, famotidine 10 mg is available as a tablet, chewable tablet, and gelcap as well as a combination chewable tablet containing calcium carbonate, magnesium hydroxide and famotidine. The 20 mg OTC product has the same indications as the 10 mg OTC product.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound alike or look alike to "Maximum Strength", since the tradename "Pepcid AC" is already in the U.S. market, to a degree where potential confusion between drug names could occur under the usual clinical

¹ MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database⁴ and the data provided by Thomson & Thomson's SAEGIS™ Online Service⁵ were also conducted. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Pepcid AC". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The panel had concerns with the need to distinguish the Pepcid AC 10 mg and the Pepcid AC 20 mg.
2. DDMAC did not have concerns about the name "Pepcid AC" with regard to promotional claims.

B. AERS SEARCH

DMETS searched the FDA Adverse Reporting System (AERS) database for any post-marketing safety reports of medication errors on "Pepcid AC". The Meddra Preferred Term (PT), "Medication Error" and the active ingredient, tradename, and verbatim for "PEP%" and "FAM%" were used to perform the searches. The search yielded no medication error reports regarding "Pepcid AC".

The FDA Drug Quality Reporting System (DQRS) database was also searched for medication error reports on "pep%" and "fam%". The search yielded no medication error reports regarding "Pepcid AC".

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the phrase "Maximum Strength", which will be used in conjunction with the proprietary name "Pepcid AC", DMETS did not find any sound and/or look-alike names to "Maximum Strength" that currently exist in the U.S. marketplace. DMETS also identified other OTC products that use a modifier to denote a different strength such as *Bayer Extra Strength*, *Junior Strength Advil*, *Triaminic Night Time Maximum Strength*, *Pepto Bismol Maximum Strength*, and *Minoxidil Extra Strength*. DMETS agrees that a modifier should be used to distinguish the 20 mg from the 10 mg product, and, therefore, has no objections to the use of "Maximum Strength" in conjunction with "Pepcid AC" for the 20 mg product. Even though DMETS finds the name "Pepcid AC Maximum Strength" acceptable, DMETS notes that it may be difficult for the sponsor to find a different modifier for a higher strength of "Pepcid AC" if a higher strength becomes available at a later time in the OTC market. Also, DMETS still has concerns that the introduction of Pepcid AC 20 mg to the OTC market might confuse the general

⁴ WWW location <http://www.uspto.gov>.

⁵ Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

public with the currently marketed Pepcid AC 10 mg since both products' packaging look very similar. Also, the strength font size on the packaging of both the 10 mg and 20 mg product is very small and hard to read. The packaging should be different enough so that a consumer would be able to distinguish between the 20 mg and the 10 mg product.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the insert pouch of "Pepcid AC Maximum Strength", DMETS has focussed on safety issues relating to possible medication errors, and has identified several areas of possible improvement, which might minimize potential user error. The container labels and carton labeling were not submitted to DMETS for review. The recommendations below also applies to any to any container labels and carton labeling associated with this product.

- A. The package insert pouch for the "Pepcid AC Maximum Strength" should look different from the 10 mg package. This could be attained by using a different color scheme on the package.
- B. The "20 mg" strength on the 20 mg product as well as "10 mg" strength on the 10 mg product are very hard to read. DMETS suggests enlarging the strength font size on both the 20 mg and the 10 mg package so that a consumer could easily read that the "Pepcid AC Maximum Strength" contains a higher strength.

**APPEARS THIS WAY
ON ORIGINAL**

IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the phrase “Maximum Strength” in conjunction with the proprietary name “Pepcid AC”.
- B. DDMAC finds the proprietary name, “Pepcid AC Maximum Strength”, acceptable from a promotional perspective.
- C. DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA supplement. A re-review of the name prior to NDA supplement approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Jennifer Fan, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Denise Toyer
4/9/03 04:02:21 PM
PHARMACIST
for Jennifer Fan

Carol Holquist
4/10/03 07:13:44 AM
PHARMACIST

Jerry Phillips
4/10/03 10:22:11 AM
DIRECTOR

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type):

NDA 20-325/S-015, Pepcid 20mg (famotidine) Maximum Strength

Applicant: **Merck Research Labs**

Date of Application: November 22, 2002

Date of Receipt: November 22, 2002

Date of Filing Meeting: January 13, 2002

Filing Date: January 21, 2003

Indication(s) requested:

Type of Application: Full NDA _____ Supplement X

(b)(1) X (b)(2) _____

[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S X P _____

Resubmission after a withdrawal or refuse to file N/A

Chemical Classification: (1,2,3 etc.) 3

Other (orphan, OTC, etc.) OTC

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid Yes Waived (e.g., small business, public health) _____

Exempt (orphan, government) _____

Form 3397 (User Fee Cover Sheet) submitted: YES X NO _____

User Fee ID# 4454

Clinical data? YES X NO _____ Referenced to NDA# 020-325

Date clock started after UN _____

User Fee Goal date: September 22, 2003

Action Goal Date (optional) _____

• Does the submission contain an accurate comprehensive index? YES NO

• Form 356h included with authorized signature? YES NO

If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? YES NO
 If no, explain:
- If electronic NDA, does it follow the Guidance? YES NO NA
If an electronic NDA: all certifications must be in paper and require a signature.
- If Common Technical Document, does it follow the guidance? YES NO NA
- Patent information included with authorized signature? YES NO
- Exclusivity requested? YES; If yes, _____ years NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, the U.S. Agent must countersign.

Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, "To the best of my knowledge,"

- Financial Disclosure included with authorized signature? YES NO
 (Forms 3454 and/or 3455)
If foreign applicant, the U.S. Agent must countersign.

* Note: Two studies S-017 and S-019 do not contain financial disclosure.

- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO
 If no, for what ages and/or indications was a waiver and/or deferral requested:

Waiver requested for less than 12 years of age. (Based on recent approval of Pepcid Complete)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

Yes

List referenced IND numbers: **I 32814**

End-of-Phase 2 Meeting? Date _____ NO
 If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)?
 If yes, distribute minutes before filing meeting.

Date(s) May 30th and June 20, 2002

Project Management

Copy of the labeling (PI) sent to DDMAC? YES NO- NA

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support? YES NO

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support? YES NO- NA

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO
Not required

Advisory Committee Meeting needed? YES, date if known _____ NO

Clinical

• If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO- NA

Chemistry

• Did sponsor request categorical exclusion for environmental assessment? YES NO
 If no, did sponsor submit a complete environmental assessment? YES NO
 If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

• Establishment Evaluation Request (EER) package submitted? YES NO

• Parenteral Applications Consulted to Sterile Products (HFD-805)? YES NO

If 505(b)(2), complete the following:

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?
 (Normally, FDA will refuse-to-file such applications.)

YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?

If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?

YES NO

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

___ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO NA

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 13, 2003

BACKGROUND

Pepcid 10mg (NDA 20-325) was approved January 25, 1993 for the treatment and prevention of heartburn in the OTC population. The sponsor, Merck Research Laboratories and Johnson and Johnson Merck Consumer Pharmaceuticals have participated in a number of regulatory meetings with the Agency to discuss a clinical development program that would support an approval of a 20mg over-the-counter Pepcid® Product. The last two meetings (May 30th, 2002, and June 20, 2002), had provided the sponsor with the general guidelines on the content of a submission as well as the statistical approaches to support an approval

ATTENDEES:

Charles Ganley, HFD-560
Andrea Segal, HFD-560
Linda Hu, HFD-560
Dan Keravich, HFD-560
Helen Cothran, HFD-560
Arlene Solbeck, HFD-560
Joyce Korvick, HFD-180
Paul Levine, HFD-180
Susan Daugherty, HFD-180
Abimbola Adebawale, HFD-880

Post Meeting Contacts for Filing Decisions

Milton Fan, HFD-715
Vespi, Bhavnagri, HFD-550

ASSIGNED REVIEWERS:

Discipline

Reviewer

Medical:	Dr. J. Korvick
Secondary Medical:	Dr. L. Hu
Statistical:	Dr. T. Permeth & Dr. M. Fan
Pharmacology:	
Statistical Pharmacology:	
Chemist:	Dr V. Bhavnagri
Environmental Assessment (if needed):	
Biopharmaceutical:	Dr. A. Adebawale, Dr. D. Bashaw
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Project Manager:	D.Keravich & P. Levine
Other Consults:	

Per reviewers, all parts in English, or English translation? YES X NO

CLINICAL – File Refuse to file _____
• Clinical site inspection needed: YES _____ NO
MICROBIOLOGY CLINICAL – File _____ Refuse to file _____ NA
STATISTICAL – File Refuse to file _____
BIOPHARMACEUTICS – File Refuse to file _____
• Biopharm. inspection Needed: YES _____ NO
PHARMACOLOGY – File _____ Refuse to file _____ NA
CHEMISTRY –
• Establishment(s) ready for inspection? YES NO _____ File Refuse to file _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

Deficiencies to be resolved in the day 74 letter to the company.

- Patent information needed 21 CFR 314.53.A
- Financial Disclosures needed for Study 17 & 19
- Study #137 in the EDR, along with Program Documentation and User Guide for Statistical Reviewing Aid for Study 137 was missing.
- Labeling discrepancies were identified.
- Clinical Safety study information may be necessary.

_____ The application is unsuitable for filing. Explain why: NA

The application was stated to be fileable. A review goal date was set for all reviews to be completed by August 1st, 2003.

HFD-180 review responsibilities- Clinical studies submitted to determine efficacy.
HFD-560 review responsibilities- Safety issues.

This supplement will require a dual division signature (HFD-180 and HFD-560).

Dan Keravich
Regulatory Project Manager, HFD-560

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Daniel Keravich
1/31/03 08:18:17 AM
CSO

David Hilfiker
1/31/03 08:52:50 AM
CSO

MEMORANDUM OF TELECON

DATE: JUNE 20, 2002

APPLICATION NUMBER: IND 32,814, Pepcid Oral Tablets

BETWEEN:

Name: Scott Korn, M.D., Senior Director, Clinical research
Robert Tipping, Associate Director – Clinical Biostatistics
Laura Stauffer, Associate Director – Clinical Biostatistics
Edwin Hemwall, Ph.D., Vice President, OTC Regulatory Affairs
Brenda McGuire, M.S., R.N., Manager, OTC Regulatory Affairs
Phone: (484) 344-7235
Representing: Merck & Co., Inc.

AND

Name:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Victor Raczkowski, M.D., M.Sc., Division Director
Hugo E. Gallo-Torres, M.D., Ph.D., Medical Team Leader, GI Drugs
Paul E. Levine, Jr., R.Ph., Regulatory Health Project Manager

Division of Biometrics II (HFD-715)

Tom Permutt, Ph.D., Statistical Team Leader

SUBJECT(S): To answer the sponsor's questions and to discuss the statistical issues concerning the development of Pepcid 20 mg for OTC use.

BACKGROUND:

On February 28, 1989, the sponsor submitted IND 32,814 for the study of Pepcid™ (famotidine) Tablets for OTC use.

In a meeting held May 30, 2002, FDA met with representatives of Merck to answer the sponsor's questions and provide guidance concerning clinical studies for the development of Pepcid 20 mg for OTC use in the treatment and prevention of moderate to severe heartburn. In that meeting the sponsor requested and was granted permission to meet with the review statistician to discuss issues related to the analyses of clinical study data for the drug.

On June 07, 2002, the sponsor submitted a background package containing 3 questions for the review statistician to answer.

THE CALL:

The Agency conveyed the following responses to the sponsor questions.

Question A. Proposed Statistical Method for Evaluating Dose Response:

We propose to evaluate dose response, for both the heartburn prevention and treatment studies, using a test of linear trend with the appropriate contrast statement. Does the Biometrics Division agree with this approach?

Agency's Response: No, we do not agree. As pointed out by Merck in the discussion, the test for trend is identical to the pairwise test of 20 mg against placebo. As such, the trend test does not address at all the comparison of 20 mg to 10 mg. Some evidence of a meaningful advantage of 20 mg over 10 mg will be required, but this evidence need not be in the form of a statistically significant difference in the primary endpoint. It might, for example, take the form discussed in Question B.

Question B. Heartburn Prevention:

Does the Biometric Division support the shift in focus from a primary to a secondary efficacy endpoint, keeping in mind that a pairwise comparison between 10 and 20 mg is no longer required to be statistically significant?

Agency's Response: Yes.

Question C. Heartburn Treatment Indication:

Does the Biometric Division agree that Agency-requested, post-hoc analyses performed on previously submitted studies can be considered for review in evaluating a treatment claim for famotidine 20 mg OTC?

Agency's Response: Yes, such analysis will be considered in review. We are aware that it was not the analysis specified in the protocols for these studies, but rather it emerged after later discussions between Merck and FDA, and it will be reviewed in this light. We have not yet gone back to review earlier submissions in detail, so we do not offer an opinion as to whether these methods will be appropriate. However, we do not object in principle to generalized estimating equation (GEE) methods.

We note, however, that GEE methods were the occasion of some controversy in the review of Merck's famotidine-antacid combination product. This was not because of objections to the

method *per se*, but because of deficiencies in the documentation. There are many choices to be made under the rubric of GEE analysis, including choice of a covariance structure, and we could not tell exactly what was done in the other application. In applying GEE methods to this application for Pepcid 20 mg OTC, it will be important to document precisely what choices were made.

Additional Discussion:

The sponsor asked whether a waiver of the disclosure of financial interests could be granted for these fairly old studies.

The sponsor was informed that the question of whether a waiver of the disclosure of financial interest would be granted could not be addressed at this time. The Agency will provide a response to the sponsor's question after reviewing the matter further.

The call was ended.

**APPEARS THIS WAY
ON ORIGINAL**

This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.

/s/

Paul Levine
8/8/02 12:43:54 PM
CSO

Victor Raczkowski
8/8/02 12:56:04 PM
MEDICAL OFFICER

Memorandum of Meeting Minutes

Meeting Date: May 30, 2002
Meeting Time: 2:30- 4:00pm
Meeting Location: POTOMAC Conference Room, Parklawn Building, 3rd floor

Application Number: IND 32,814, Pepcid™ OTC Tablets
Nonprescription famotidine tablets

Type of Meeting: Industry Meeting
Meeting Chair: Victor Raczkowski, M.D., M.Sc.
Meeting Recorder: Paul E. Levine, Jr., R.Ph.

List of FDA Attendees

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Victor Raczkowski, M.D., M.Sc., Division Director
Joyce Korvick, M.D., M.P.H., Deputy Division Director
Hugo E. Gallo-Torres, M.D., Ph.D., Medical Team Leader, Gastrointestinal Drugs
Paul E. Levine, Jr., R.Ph., Regulatory Project Manager

Division of Over the Counter Drug Products (HFD-560)

Charles Ganley, M.D., Director
Linda Katz, M.D., M.P.H., Deputy Director
Helen Cothran, Team Leader
David Hilfiker, Supervisory Consumer Safety Officer
Walter Ellenberg, Ph.D., Regulatory Project Manager

External Constituents:

Merck Research Laboratories

Robert Tipping, Associate Director – Clinical Biostatistics
Laura Stauffer, Associate Director – Clinical Biostatistics
Marriane Villani, Senior Medical Program Coordinator
Stephanie Levy, Director – Consumer Research
Jerry Hansen, Vice President, New Products Development
Marie Dray, Executive Director, Regulatory Agency Relations
Scott Korn, M.D., Senior Director, Clinical research
Juli Miller, Manager, Consumer Research
Cynthia Guzzo, M.D., Director, Clinical Research
Renaat Van den Hooff, Vice President, Base Business
Terry Merkle, Director, New Products Development
John Irvin, Ph.D., Vice President, Clinical & Regulatory Development

_____, M.D., Consultant, Professor of Medicine, Division of Gastroenterology,

School of Medicine
Edwin Hemwall, Ph.D., Vice President, OTC Regulatory Affairs
Brenda McGuire, M.S., R.N., Manager, OTC Regulatory Affairs

BACKGROUND

On February 28, 1989, the sponsor submitted IND 32,814 for the study of Pepcid™ (famotidine) Tablets for OTC use.

In meetings held December 10, 1997, and December 16, 1998, representatives of Merck and FDA discussed the clinical development of famotidine OTC for the treatment and prevention of moderate to severe heartburn.

On August 7, 2001, FDA met with representatives of Merck to answer the sponsor's questions and provide guidance concerning the results of clinical studies for the development of famotidine 20 mg for OTC use in the treatment and prevention of moderate to severe heartburn.

On February 20, 2002, the sponsor submitted a meeting request to discuss additional issues related to the development of famotidine 20 mg for OTC use.

MEETING PURPOSE

To answer sponsor's questions and provide guidance concerning the clinical development of famotidine 20 mg for OTC use.

DISCUSSION

Response to Sponsor's Questions

Question #1: In initial meetings with the Agency (12/97 and 12/98) to discuss the famotidine 20 mg OTC program, the FDA directed that a distinct population must be identified that would benefit from this product, and agreed that those with severe heartburn might be an acceptable population. Subsequently, at our most recent meeting (8/7/01) FDA re-directed that this population is not appropriate. Precedent exists for approval through the NDA process of a higher strength OTC product based on demonstration of superior efficacy without defining a different population. We have clinical data from one study (Protocol 117) demonstrating superior efficacy of famotidine 20 mg over famotidine 10 mg for the prevention of heartburn. Therefore, we believe that, in the absence of a proven safety concern, a second

study with similar results, in the general OTC heartburn population, should support approval of the 20 mg dose for OTC use.

Does the Agency accept, in principle, that a demonstration of statistically greater efficacy of famotidine 20 mg over 10 mg and placebo, for the prevention of heartburn in a general OTC heartburn population, could support approval of a 20 mg product?

Agency's Response: Prevention of heartburn by famotidine 20 mg over famotidine 10 mg and over placebo in the same population should be clinically meaningful, not simply statistically significant.

In addition, clarify why you are seeking just the prevention claim. The 20 mg famotidine product would also treat heartburn symptoms and might work better than famotidine 10 mg. You may want to test for the effectiveness in the treatment of immediate symptoms in addition to prevention of future symptoms. This is important so that consumers who use Pepcid AC or Pepcid Complete for relief do not think they need to purchase famotidine 20 mg for prevention. If the same population will be targeted by both famotidine 10 mg and famotidine 20 mg, then it would make sense for the indications for the 20 mg dose to be treatment and prevention, similar to the Pepcid AC product.

Additional Discussion: The sponsor presented slides showing data for the percentage of patients reporting complete prevention, comparison of the effect of Pepcid 20mg and 10mg doses on peak heartburn, and comparison of complete relief from original NDA treatment studies. (See attached slides)

The sponsor asked if it was necessary to show a statistically significant difference between the 20mg and the 10mg doses of Pepcid for use in the prevention of heartburn. The sponsor was informed that it was not necessary to show a statistically significant difference between the two doses. The Agency recommended the study of various doses with placebo to illustrate a linear trend in dose response between 10 mg and 20 mg. The sponsor was also informed that efficacy should be based upon a clinical meaningful endpoint.

Question #2. We propose to submit two pivotal heartburn prevention studies designed according to standards established for the approval of all OTC H₂RAs, to support the approval of famotidine 20 mg OTC. The first is Study 117, a multicenter trial that was conducted to evaluate the efficacy of 20 mg famotidine for prevention of heartburn in those that had severe heartburn at least 30% of the time. The results demonstrated a statistically superior and clinically meaningful difference of 20 mg

famotidine over 10 mg famotidine for the prevention of heartburn. The second study, similar in design to Study 117, will be a multicenter provocative meal trial to demonstrate the superior efficacy of 20 mg famotidine relative to 10 mg and placebo, for prevention of heartburn. The target population will include those individuals with any severity of heartburn by history (see Section IX for study design).

Are Study 117 and the newly proposed second efficacy study acceptable to evaluate famotidine 20 mg for the heartburn prevention indication?

Agency's Response: If the same population as Pepcid AC will be targeted for the famotidine 20 mg product, then we suggest you perform a second study consisting of an efficacy trial for treatment of acute heartburn, rather than conducting another prevention trial.

If more than 1 dose of famotidine 20 mg per day for up to 14 consecutive days for prevention will be recommended, you should demonstrate in the proposed study the rationale for choosing an 8-hour time interval between doses for heartburn prevention. Previous studies with these doses were for treatment of PUD, and GERD with and without erosive esophagitis. The 8-hour time interval may not be the best for "heartburn." Perhaps one dose/day of 20 mg will be as good as two doses for heartburn prevention.

Additional Discussion: The sponsor asked if the Agency would view protocol #117 as a pivotal study with additional study data being used in support of this study. The sponsor was informed that the Agency is interested in receiving additional data concerning the proposed prevention indication. Whether or not protocol #117 would be considered a pivotal study is an issue for review.

Question #3. The enclosed label (Section VII) was developed after the conduct of focus groups and a pilot label comprehension study. The label was designed specifically to direct individuals to use famotidine 20 mg for prevention only, and to identify other important medical issues, including dosing interval and circumstances when a physician should be consulted. We believe this approach can address concerns raised by the Agency at our last meeting. Further, results of the pilot label comprehension study indicate that the directions are generally well understood by consumers (Section VI).

While we recognize the need for further refinement and therefore plan to conduct a pivotal label comprehension study, does the Agency have any comments or suggestions to offer at this time on the enclosed draft Drug Facts label?

Agency's Response: The label comprehension study would not be considered as a pivotal trial. The actual use study might be considered a pivotal trial.

Additional Comments on the Label:

- The label tells consumers that they can use the product to prevent heartburn and sour stomach. Even though, the indication is not stomach pain relief or prevention, the label states to stop use if stomach *pain* continues. The label should be modified to more accurately reflect the condition being treated and the adverse events that might signal the need for additional medical intervention.
- The label does not tell consumers what to do if they use the product to prevent symptoms for 14 days and symptoms recur after the product is discontinued.
- At the 20 mg to 40 mg/daily dose a renal warning might be necessary.
- Clarify the rationale for recommending that consumers need more than one daily dose and should allow at least 8 hours between doses.

Additional Discussion: The sponsor stated that it did not think a renal warning for Pepcid is necessary. The sponsor acknowledged changes in the prescription product in response to the Agency's request, but could find no supportive evidence for requiring a renal warning for Pepcid products.

The sponsor was referred to the letter dated October 03, 2000, in which the Agency, after reviewing literature reports and based on the evaluation of the pharmacokinetic and pharmacodynamic properties of Pepcid, requested that the "Dosage Adjustment for Patients with Severe Renal Insufficiency" subsection under the DOSAGE AND ADMINISTRATION section be revised to reflect the need for dosage adjustment in patients with both moderate (creatinine clearance less than 50ml/min) and severe renal impairment. The supplements for the requested changes were submitted on December 20, 2000, and approved on March 14, 2001. The sponsor was informed that additional study data concerning the use of Pepcid in renally impaired patients could be submitted to the Agency for review. The Agency would consider changes to the labeling if validated by the reviewed data.

Question #4. As directed by the Agency at our last meeting, we plan to conduct a Use Study that we believe will demonstrate that most individuals will choose to use famotidine 20

mg OTC for episodic prevention of heartburn (as opposed to relief of symptoms) and will follow label directions when using the product. An outline of the proposed study is included in Section IX.

Does the Agency have any comments on the design of the Use Study?

Agency's Response: If famotidine 20 mg were indicated for both the prevention and relief claims like Pepcid AC, then an actual use study would not be necessary. However, there is concern about the safety of the higher dose for patients with renal insufficiency because of delayed drug clearance. You would need to provide data to demonstrate that this would not be a worry if the higher dose went over-the-counter. If you do not already have this data, it could be obtained by performing a pharmacokinetics/pharmacodynamics study looking at safety of famotidine 20 mg/day and 40 mg/day in patients with renal insufficiency.

Comments on the Actual Use Study Proposed in this submission:

- A primary objective of this trial should be to determine whether participants properly self-select to use famotidine 20 mg based upon the warnings. Since the 20 mg product targets the same population and is for the same prevention indication as the 10 mg product, the only self-selection issue for indication would be whether the participant is looking for heartburn treatment instead of prevention.
- Provide data on the use of famotidine 20 mg and 40 mg/day in renal impairment patients. If it would be dangerous for people with renal impairment to take famotidine 20 mg or 40 mg daily, such that this population would be excluded, then it should be demonstrate in the actual use study that people with renal impairment know they have this condition and do not self-select to take the drug. A renal warning should be on the label. In addition, you should obtain baseline renal function tests on all participants and permit the self-selection step to occur in all participants. You might provide a listing of medical conditions on the label that are frequently associated with renal insufficiency (e.g., diabetes mellitus, hypertension) and determine if this assists the consumer in the self-selection process.
- For the study to be as naturalistic as possible, participants should be allowed to obtain as much medication as they want at any time during the study, including the initial visit.
- Participants should record use of all concomitant medications not just those specified as stomach remedies.

- The 5-point efficacy scale should be the same scale as is to be used in the efficacy study to measure global assessment.
- Compliance with label directions should also include not using the product for more than 14 days in a row.
- The target of participants taking 70% of doses for prevention is low. If the label is clearly written, then a much higher percentage of doses should be for the appropriate indication. You should determine the percentage of participants who always use famotidine 20 mg for prevention.
- Compliance with the label should also mean appropriate self-selection with regard to indications, contraindications, and warnings and use of appropriate or inappropriate concomitant medications.
- Clarify what number of participants you actually plan to enroll? You propose to enroll 500 participants with episodic heartburn, yet the proposal estimates that a sample size of 400 patients is sufficient to estimate 95% confidence intervals with a width less than or equal to 9.8 percentage points for the true percentages for the noncompliance parameters.

ADDITIONAL DISCUSSION

We have the following comments and suggestions concerning your proposed labeling:

1. In *Uses*, add a relief indication depending on what population will be targeted.
2. In *Uses*, a statement clarifying the target population may help consumers to correctly select/deselect, such as “ _____ ” (or whatever the target population is).
3. Add a general heartburn warning, for example: “ _____ ”
_____” This warning would be placed directly below the “allergy alert”.
4. Do not include proprietary drug product names in the Drug Facts labeling.

5. Add the section _____ (after the **Do not use** section) to list kidney disease. Also consider listing in this section _____

Although this is not currently required for OTC acid reducer drug products, all other companies will eventually be asked to do this (proposed class labeling).
6. In the section **Stop use and ask a doctor if**, consider revising the second bullet to read “ _____ ”. Consider replacing the fourth bullet with a more direct statement that tells consumers when to see a doctor such as “ _____ ”.
7. In *Directions*, add a direction for relief if the indications include this claim.

CONCLUSION

1. The sponsor will consider comments by the Agency and modify current studies as necessary.
2. The Project Manager will facilitate a meeting between the review statistician and the sponsor to discuss details for proposed study analyses. After the meeting the sponsor will submit a proposal for data analyses.

Attachments:

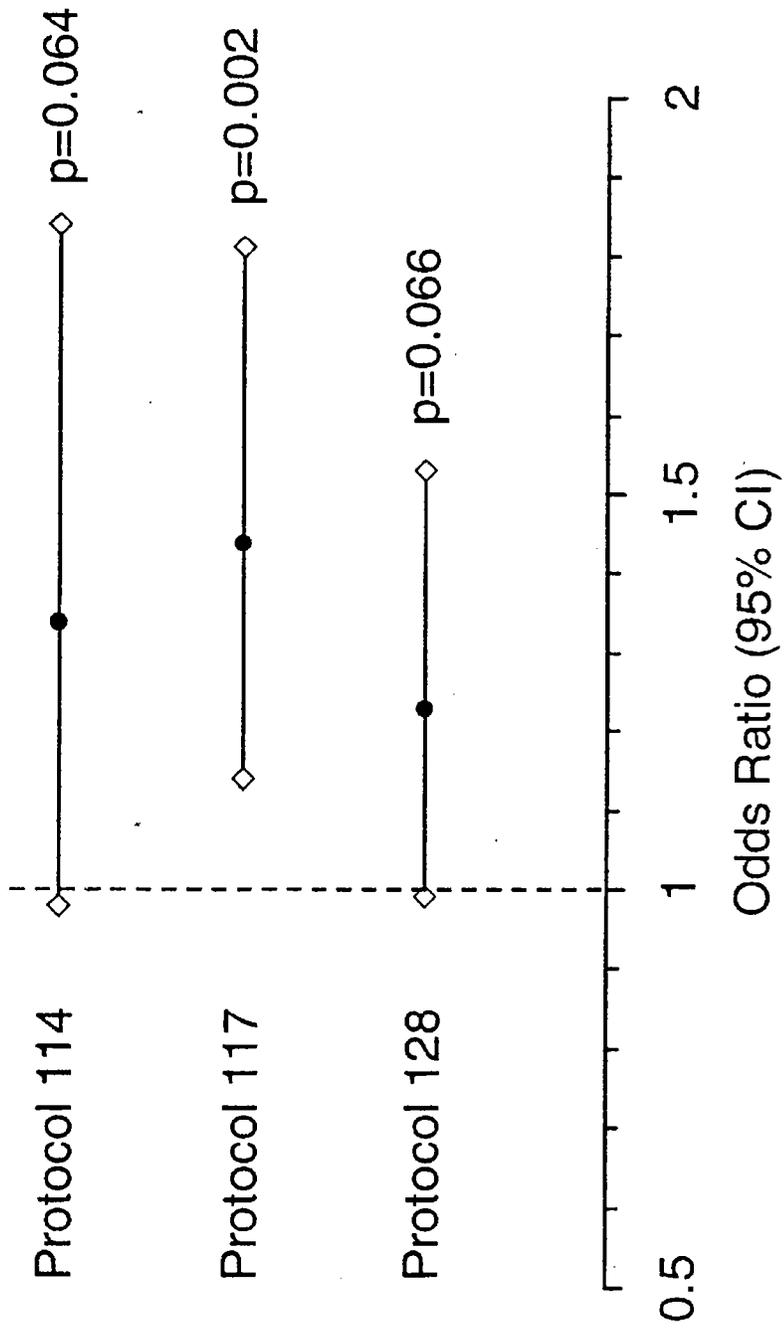
**APPEARS THIS WAY
ON ORIGINAL**

Attachment

Percentage of Patients Reporting Complete Prevention

% of Patients Reporting Complete Prevention				
Protocol	N	FAM 20 mg	FAM 10 mg	Placebo
114	794	11% *	8%	4%
117	1227	38% * F	30% *	19% *
128	1332	41% * F	35% *	27%
* $p \leq 0.05$ vs placebo				
F $p \leq 0.05$ vs famotidine 10 mg				

Peak Heartburn Famotidine 20 mg vs. Famotidine 10 mg



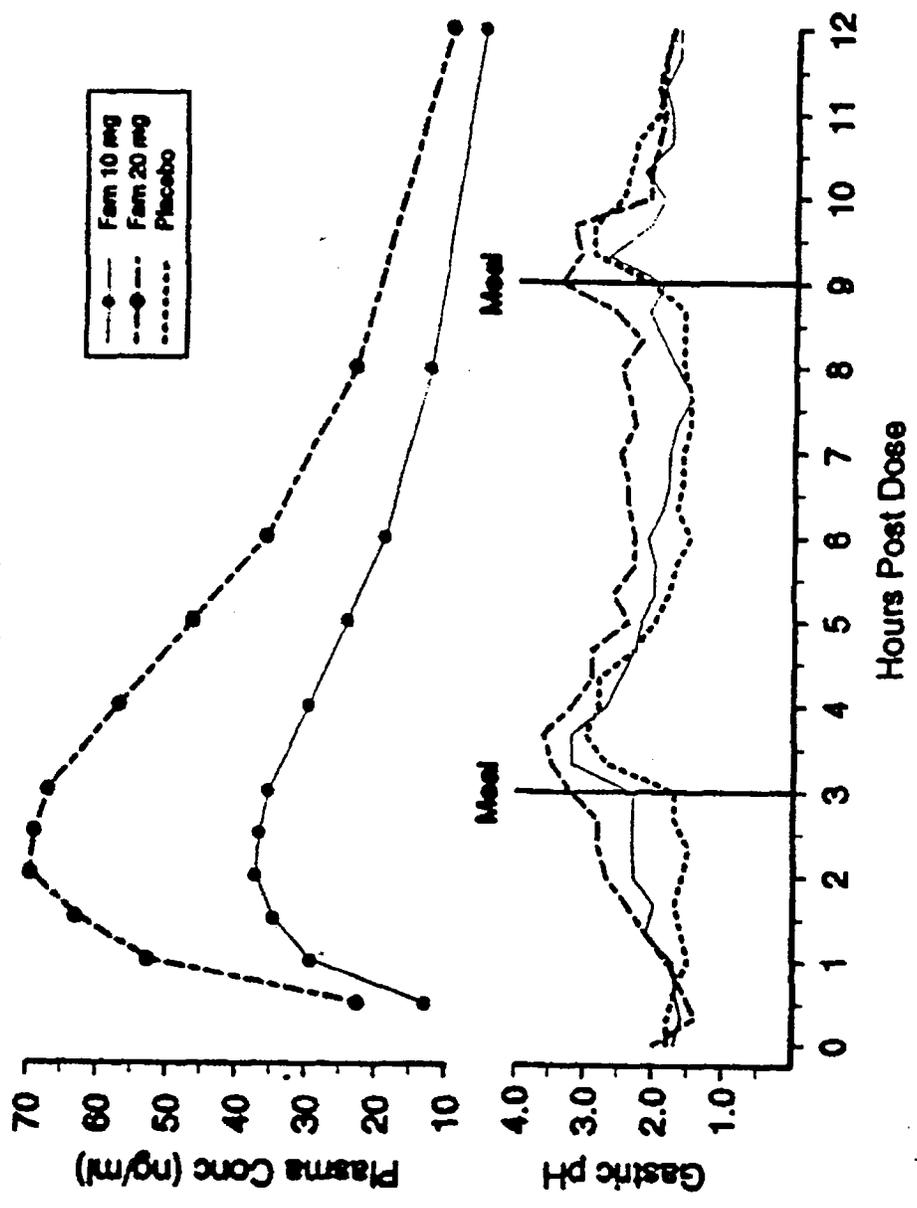
Complete Relief Original NDA Treatment Studies

	n	Mean % of Episodes Completely Relieved Within		
		1 Hour	2 Hours	3 Hours
Protocol 017				
FAM 20 mg	113	39.3%	52.2%	59.7%
FAM 10 mg	109	35.0%	48.2%	58.0%
Placebo	109	25.4%	34.8%	43.0%
Protocol 019				
FAM 20 mg	129	37.4%	51.3%	58.3%
FAM 10 mg	122	33.2%	48.9%	56.9%
Placebo	128	24.6%	40.6%	49.8%

Complete Relief Within 1 Hour Original NDA Treatment Studies

Proportion of Heartburn Episodes Completely Relieved Within 1 Hour			
Protocol		FAM 20 mg vs Placebo	FAM 10 mg vs Placebo
017 (N=553)	Odds-Ratio p-value	2.01 <0.001	1.72 0.003
019 (N=500)	Odds-Ratio p-value	2.05 <0.001	1.73 <0.001

PK/PD Protocol 021 (Famotidine Powder 10 mg & 20 mg)
(N=18)



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-325 / S-015

CORRESPONDENCE



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-325/S-015

Merck & Co, Inc.
Attention: Brenda McGuire, M.S., R.N.
Associate Director – Worldwide OTC Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLX-29
West Point, PA 19486

Dear Ms. McGuire:

We refer to your submission dated November 11, 2002, requesting a waiver for pediatric studies for Pepcid AC (20 mg famotidine) Tablets.

We have reviewed the submission and agree that a waiver is justified for Pepcid AC (20mg famotidine) Tablets for prevention and treatment of heartburn for consumers 12 years of age or younger because there are too few persons in this age range with the disease to study.

Accordingly, at this time, a waiver for pediatric studies for your application is granted under section 2 of the Pediatric Research Equity Act.

If you have questions, call LCDR Keith Olin, Regulatory Project Manager, at 301-827-2293.

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Charles Ganley
7/12/04 03:28:35 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-325/S-015

Merck & Co., Inc.
Attention: Brenda A. McGuire, M.S., R.N.
Associate Director, OTC Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLX-29
West Point, PA 19486

Dear Ms. McGuire:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pepcid Maximum Strength (20mg famotidine) Tablets. The Pediatric Research Equity Act ("PREA") was enacted on December 3, 2003. PREA provides that for applications submitted between April 1, 1999, and December 3, 2003, where pediatric studies were not submitted with the application and neither a waiver nor a deferral of pediatric studies was granted under the regulations in effect at the time the application was submitted, the applicant must obtain a waiver or must submit studies by the later of December 3, 2004, or a date specified by the Agency in response to a request for a deferral. Your application, dated November 22, 2002, was submitted without pediatric studies. Further, you were not granted a waiver or a deferral of pediatric studies under the regulations in effect at the time this application was submitted. Under PREA, please submit the required pediatric assessments by December 3, 2004. If you believe your application qualifies for a waiver or deferral of pediatric studies under PREA, submit a letter requesting waiver or deferral and stating the basis for your request within 60 days of the date of this letter.

If you have any questions, call LT Keith Olin, Regulatory Project Manager, at 301-827-2293.

Sincerely,

{See appended electronic signature page}

Charles Ganley, MD
Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

David Hilfiker
6/7/04 03:45:08 PM
For C. Ganley



NDA 20-325/S-015

Merck & Co., Inc.
Attention: Edwin Hemwall, Ph.D.
Vice President
Global Regulatory Affairs
Sumneytown Pike, P.O. Box 4
BLA-29
West Point, PA 19486

Dear Dr. Hemwall:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pepcid AC (10 and 20 mg famotidine) Tablets, approved on September 23, 2003.

During the review of this supplemental NDA, we provided you with comments on the proposed labeling in a facsimile correspondence dated July 14, 2003. Comment A.1. in this facsimile requested that you remove the phrase "_____ " from the labeling. On August 6, 2003, you submitted new proposed labeling under this supplemental NDA that complied with this request. Your labeling dated August 6, 2003, is considered to be the approved labeling for this product.

This serves to follow-up on the September 23, 2003, approval letter, regarding the use of the phrase "_____ " in your product labeling.

Although the phrase is factually correct, it is potentially misleading and may lead to consumer abuse of this product. Identical formulations under the trade name Pepcid are now available over-the-counter for the treatment of heartburn episodes and by prescription only for the treatment of related conditions that require physician diagnosis and monitoring. By promoting the term "_____ " for an OTC product that coexists as a prescription product under the same trade name, there is potential that consumers familiar with the prescription uses will abuse the OTC availability of this product, ignoring the limitations on duration of use and/or frequency of use to self-treat conditions that should be evaluated by a physician. Therefore, if you have an interest in incorporating the phrase "_____ " on the labeling for this product in the future, we encourage you to contact the Division of Over the Counter Drug Products to further discuss this proposal.

NDA 20-325/S-015

Page 2

If you have any questions, call Laura Shay, Regulatory Project Manager, at 301-827-2274.

Sincerely yours,

{See appended electronic signature page}

Charles Ganley, M.D.

Director

Division of Over-the-Counter Drug Products

Office of Drug Evaluation V

Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Charles Ganley
1/29/04 03:52:00 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Division of OTC Drug Products
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: September 23, 2003

To: Brenda MacGuire	From: Laura Shay, MS, RN, C-ANP Regulatory Project Manager
Company: Merck	Division of Over-the-Counter Drug Products
Fax number: 484-344-3682 (2613)	Fax number: (301) 827-2315
Phone number: 484-344-7235	Phone number: (301) 827-2274
Subject: September 22, 2003, T-con summary	

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2222. Thank you.

Please refer to your supplemental new drug application NDA 20-325/S-015 dated February 25, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pepcid AC.

The following is a summary of the teleconference held today, September 22, 2003:

1. Due to the federal government closing on September 18, and 19, 2003, a 2 day extension of the PDUFA goal date may be requested. The Division committed to acting on the application on or before September 24, 2003.
2. The possibility of a Phase IV commitment for a clinical study looking at effectiveness in non-Caucasian persons was discussed.
3. Merck was informed that there are additional discussions with the Division of Gastrointestinal and Coagulation Drug Products on the evidence supporting a dose response for treatment that need to occur before the action can be generated.

Attendees to the T-con included:

Division of Over-the-Counter Drug Products:

Charles Ganley, M.D., Division Director
Dave Hilfiker, M.S., Chief Project Management Staff
Laura Shay, M.S, R.N., C-ANP, Regulatory Project Manger

Merck:

Brenda McGuire, M.S., R.N., Associate Director, Worldwide OTC Regulatory Affairs
Robert Tipping, Associate Director, Clinical Biostatistics
Jeffery Levine, M.D., Senior Director, Clinical Research
Edwin Hemwall, Ph.D., Vice President, Global Regulatory Affairs

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Laura Shay
9/23/03 03:26:07 PM
UNKNOWN



Food and Drug Administration
Center for Drug Evaluation and Research
Division of OTC Drug Products
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: July 14, 2003

To: Brenda MacGuire	From: Laura Shay, MS, RN, C-ANP Regulatory Project Manager
Company: Merck	Division of Over-the-Counter Drug Products
Fax number: 484-344-3682 (2613)	Fax number: (301) 827-2315
Phone number: 484-344-7235	Phone number: (301) 827-2274
Subject: Labeling Comments	

Total no. of pages including cover:

Comments:

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2222. Thank you.

Please refer to your supplemental new drug application NDA 20-325/S-015 dated February 25, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pepcid AC.

We have attached the reviewer's comments related to the labeling submitted. These labeling comments reflect our current knowledge about "MAXIMUM STRENGTH Pepcid AC". The medical officers' safety and efficacy reviews are still in progress. Additional labeling modifications may be necessary once the reviews are completed.

A. Carton Labeling (Principal Display Panel, sides, top, bottom)

1. Remove the words " _____".
2. Remove the phrase " _____" and replace with the phrase "**Prevents & Relieves Heartburn** due to Acid Indigestion" to be consistent with prior approved Pepcid labeling. Unbold words "**Prevents**" and "**Heartburn**".
3. The phrase " _____" is not clear. To provide clarity and to be consistent with the prior approved Pepcid labeling change it to "JUST ONE PER DOSE!". The phrase should also be in a smaller font size and moved so that it does not appear to be part of the brand name.
4. In accordance with 21 CFR 201.61, we suggest that the font size of the statement of identity be enlarged so that it is reasonably related to the most prominent printed matter on the PDP and so a consumer can easily read that the "Maximum Strength Pepcid AC" contains a higher strength. We recommend that the font size be at least 1/2 the size of the brand name in all the labeling.
5. We remind you that the word "NEW!" should be removed after 180 days of OTC marketing.

B. Drug Facts

1. Under *Warnings*, we recommend that the bulleted statement "if you have trouble swallowing" remain under "**Do not use**" in order to be consistent with prior approved Pepcid labeling. In addition, revise this bulleted statement to read "if you have trouble _____ swallowing _____" in order to be in accordance with the recently approved Prilosec OTC labeling.

2. Under **Warnings**, the subheading " _____ " is not an approved subheading (21CFR 201.66). In addition, the bulleted statements are not correctly aligned (21 CFR 201.66 (d)(4)). Replace the proposed subheading with the following two approved subheadings: " _____ ", and "**Stop use and ask a doctor if**". The bulleted statements can be divided between the two subheadings. Below is an example of the Agency's recommended changes to the **Warnings** section of Drug Facts. Also shown below are three examples of the recommended changes to the alarm symptoms using the language recommended for Prilosec OTC labeling as well as recommendations for kidney and CNS warnings.

**Agency's recommended *Warning* section of Drug Facts
(example 1)**

<p>Warnings</p> <p>Allergy alert Do not use if you are allergic to famotidine or other acid reducers</p> <hr/> <p>Do not use</p> <ul style="list-style-type: none">■ if you have _____<ul style="list-style-type: none">■ trouble _____ swallowing _____■ with other acid reducers <hr/> <div style="border: 1px solid black; width: 100%; height: 100%;"></div> <hr/> <p>Stop use and ask a doctor if _____</p> <ul style="list-style-type: none">■ you need to take this product for more than 14 days <hr/> <p><small>If pregnant or breast-feeding, ask a health professional before use. Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.</small></p>
--

**APPEARS THIS WAY
ON ORIGINAL**

**Agency's recommended *Warning* section of Drug Facts
(example 2)**

<p>Warnings</p> <p>Allergy alert Do not use if you are allergic to famotidine or other acid reducers</p> <p>Do not use</p> <ul style="list-style-type: none">■ if you have _____<ul style="list-style-type: none">■ trouble _____ swallowing _____ ■ with other acid reducers _____ <p>_____</p> <p>_____</p> <p>_____</p> <p>Stop use and ask a doctor if</p> <ul style="list-style-type: none">■ you need to take this product for more than 14 days <p>_____</p> <p>If pregnant or breast-feeding, ask a health professional before use. Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.</p>

**Agency's recommended *Warning* section of Drug Facts
(example 3)**

<p>Warnings</p> <p>Allergy alert Do not use if you are allergic to famotidine or other acid reducers</p> <p>Do not use</p> <ul style="list-style-type: none">■ if you have trouble _____ swallowing _____ ■ with other acid reducers _____ <p>_____</p> <p>_____</p> <p>_____</p> <p>Stop use and ask a doctor if</p> <ul style="list-style-type: none">■ you need to take this product for more than 14 days <p>_____</p> <p>If pregnant or breast-feeding, ask a health professional before use. Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.</p>
--

3. The format used for the **Directions** section is not in accordance with 21 CFR 201.66 for the **50 tablet carton**. This section is written in column format with the second sub-bulleted statement continuing onto the next line which is not acceptable under the regulations. If you wish to consider using a column format for Drug Facts, we refer you to the guidance for using a column format for labeling OTC human drugs at <http://www.fda.gov/cder/guidance/index.htm>.
4. Under **Directions**, we suggest adding the phrase "Do not chew" at the end of the first sub-bulleted statement in order to be consistent with the package insert.
5. For consistency with the Office of New Drug Chemistry recommendations, the storage statement should read "store at 20-25°C (68-77°F)". However, the 20-30°C temperature range may be used if supported by data.

C. Sample Pouch label

Our recommended changes for the **Drug Facts** labeling are also applicable to the sample pouch labeling.

D. 50-count container label

Our recommended changes for the **Drug Facts** labeling are also applicable to the container labeling.

E. Package Insert

Revise the section "**Know when to see your doctor**" to be consistent with the changes recommended for the Drug Facts carton labeling under the subheadings "**Do not use**", "**_____**", and "**Stop use and ask a doctor if**".

Again we remind you that these labeling comments reflect our current knowledge about "MAXIMUM STRENGTH Pepcid AC". The medical officers' safety and efficacy reviews are still in progress. Additional labeling modifications may be necessary once the reviews are completed.

F. Sample Drug Facts label: See attached.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Laura Shay
7/14/03 03:20:23 PM
UNKNOWN

**Sample Drug Facts Labeling for MAXIMUM STRENGTH Pepcid AC
(Famotidine 20 mg)**

*This is to provide content information only. The font sizes for titles, headings, subheadings, condensed text, bullets, and other graphic features must be in accordance with 21 CFR 201.66
Note: The Warnings section contains example 2.*

Drug Facts	
Active ingredient (in each tablet) Famotidine 20 mg	Purpose Acid reducer
Uses	
<ul style="list-style-type: none"> ■ relieves heartburn associated with acid indigestion and sour stomach ■ prevents heartburn associated with acid indigestion and sour stomach brought on by eating or drinking certain food and beverages 	
Warnings	
Allergy alert Do not use if you are allergic to famotidine or other acid reducers	
Do not use	
<ul style="list-style-type: none"> ■ if you have <ul style="list-style-type: none"> ■ trouble swallowing 	
<ul style="list-style-type: none"> ■ with other acid reducers 	
<div style="border: 1px solid black; height: 100px; width: 100%;"></div>	
Stop use and ask a doctor if	
<ul style="list-style-type: none"> ■ you need to take this product for more than 14 days 	
If pregnant or breast-feeding, ask a health professional before use	
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.	
Directions	
<ul style="list-style-type: none"> ■ adults and children 12 years and over: <ul style="list-style-type: none"> ■ to relieve symptoms, swallow 1 tablet with a glass of water. Do not chew. ■ to prevent symptoms, swallow 1 tablet with a glass of water before eating food or drinking beverages that cause heartburn ■ do not take more than 2 tablets in 24 hours ■ children under 12 years: ask a doctor 	
Other information	
<ul style="list-style-type: none"> ■ read the directions and warnings before use ■ keep the carton and package insert. They contain important information. ■ store at 20-25°C (68-77°F) ■ protect from moisture 	
Inactive ingredients carnauba wax, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, pregelatinized starch, talc, titanium oxide	
Questions or comments? 1-800-775-4008	

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Laura Shay
7/14/03 03:23:34 PM
UNKNOWN



Food and Drug Administration
Center for Drug Evaluation and Research
Division of OTC Drug Products
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: July 10, 2003

To: Brenda MacGuire	From: Laura Shay, MS, RN, C-ANP Regulatory Project Manager
Company: Merck	Division of Over-the-Counter Drug Products
Fax number: 484-344-3682 (2613)	Fax number: (301) 827-2315
Phone number: 484-344-7235	Phone number: (301) 827-2274
Subject: Data requests	

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2222. Thank you.

Please refer to your supplemental new drug application NDA 20-325/S-015 dated February 25, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pepcid AC.

HFD 180 Statistician requests additional information for comparing 10 mg vs 20 mg Pepcid for the treatment of heartburn for studies 017 and 019:

It is unclear whether the proportion of heartburn episodes completely relieved within 1 hour was with or without use of additional double-blind medication or a backup antacid. To clarify please perform:

1. A statistical analysis of pairwise comparisons among famotidine 20 mg, famotidine 10 mg and placebo for proportion of episodes completely relieved within 1, 2, and 3 hours without use of additional double-blind medication or backup antacid.
2. A statistical analysis of pairwise comparisons among famotidine 20 mg, famotidine 10 mg and placebo for proportion of episodes completed relieved within 1, 2, and 3 hours without use of additional double-blind medication or backup antacid by baseline heartburn severity.
3. Also Provide the SAS dataset and SAS programs.

HFD 560 Medical Officer requests the following:

Please provide the CRF and narrative summaries for

- the subject in Study 117 who had the adverse event of "Pain, chest"
- the subjects in Study 119 (Use study) who had the adverse events of "Pain, chest" and "Blood pressure increased"

Please provide narrative summaries on the serious cases described within the references on worldwide product safety reports (from the Nov 22, 2002 submission) for the following adverse events:

Torsade de pointes
Electrocardiogram QT prolonged
Cardiorespiratory arrest or cardiac arrest
Rhabdomyolysis
Drug interaction

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Laura Shay
7/10/03 02:23:03 PM
UNKNOWN



Food and Drug Administration
Center for Drug Evaluation and Research
Division of OTC Drug Products
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: June 19, 2003

To: Brenda McGuire	From: Laura Shay, MS, RN, C-ANP Regulatory Project Manager
Company: Merck	Division of Over-the-Counter Drug Products
Fax number: 484-344-3682 (2613)	Fax number: (301) 827-2315
Phone number: 484-344-7235	Phone number: (301) 827-2274
Subject: Data re-organization	

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2222. Thank you.

In order to expedite the review process for your supplemental new drug application NDA 20-325/S-015, please provide us data in the following format:

Provide a detailed assessment of the safety data for famotidine with regard to hematologic disorders. Evaluate if there is a dose relationship for adverse events such as thrombocytopenia, neutropenia, and pancytopenia. In this assessment, include the calculation of incidence rates per exposure and per person-years of exposure for all serious and all AEs reported by health care professionals for the events listed below, and classify reports by total oral daily dose (up to 20 mg/d vs 40 mg/d). Please reclassify, by total daily dose, the cases previously submitted including cases now classified as "miscellaneous/other" dosage. Number of deaths vs total oral daily dose should also be provided.

Tabulate and summarize hematologic data from your world-wide safety database indicating total cases, number serious cases, and deaths separated according to total oral daily dosage received (up to 20 mg/d vs 40 mg/d).

Please determine incidence rates for:

- All cases with thrombocytopenia
- Cases with one or more of bone marrow depression, myelosuppression, pancytopenia, aplastic anemia
- Cases with one or more of leukopenia, neutropenia, granulocytopenia, agranulocytosis

Provide OTC and Rx marketing data for non-USA Pepcid and total famotidine, prescription and non-prescription, preferably the same as for the datasets provided in ref 8 of the 11-22-02 submission. The number of prescriptions for famotidine should be broken down by dose--for both US and non US (data from Japan is of interest).

If you have any questions you can call Laura Shay, Regulatory Project manager, at 301-827-2274.

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Laura Shay
7/28/03 05:19:32 PM
UNKNOWN

DESK COPY

April 2, 2003



Charles Ganley, M.D. Director
Division of Over-the-Counter Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Ganley:

**NDA 20-325/S-015: PEPCID™ AC Film Coated Tablets
(nonprescription famotidine 20 mg)**

Response to FDA Request for Information

(Financial Disclosure Information)

Reference is made to the supplemental New Drug Application cited above for PEPCID™ AC submitted as an electronic archive on November 21, 2002 by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. and Johnson & Johnson ◦ Merck Consumer Pharmaceuticals Co., (JJCPC). This Prior Approval Supplement provides for a 20 mg PEPCID™ AC over-the-counter (OTC) product. Reference is also made to your letter dated January 31, 2003, issue number 2, requesting financial disclosure information for studies 017 and 019. This is the final item of the 8 items listed in the Agency's January 31st letter to be addressed.

With this communication, we are providing an explanation of the financial search conducted with regard to the clinical investigators who participated in PEPCID™ studies 017 and 019. Since these studies were completed prior to the effective date of the Final Rule on Financial Disclosure Information, Merck does not have previously collected financial disclosure information in its financial databases from the study investigators. However, as noted in the Agency's January 31st letter, the information required is limited to outcome payments and proprietary interests, which should be available to the sponsor, and should not require solicitation of that information from study investigators at the present time. As provided in the attachment, Merck & Co., Inc., has performed an internal company search of relevant databases and has determined that no outcome payments or proprietary interests existed for any of the investigators involved with either study 017 or study 019.

This amendment is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs*. As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one (1) Compact Disk (CD) which contains the amendment. All documents requiring signatures for certification are included as paper for archival purposes.

A list of reviewers from the Division of Over-the-Counter Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Mr. Dan Keravich, Regulatory Project Manager, Division of Over-the-Counter Drug Products.

All of the information is contained on one (1) CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 7.51, Symantec Corp., 2000) and we authorize the use of anti-virus software, as appropriate.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Brenda A. McGuire, M.S., R.N. (484-344-7235) or, in my absence, Edwin L. Hemwall, Ph.D. (484-344-2306).

Sincerely,



Brenda A. McGuire, M.S., R.N.
Associate Director
OTC Regulatory Affairs

Attachment
Enclosure: CD

Federal Express #1

Desk Copies: Mr. Dan Keravich
Regulatory Project Manager
HFD 560, CRP2, Room S214
Federal Express #2

**Response to FDA Request for Financial Disclosure Information on Clinical
Investigators Who Participated in PEPCID™ Studies 017 or 019**

In the January 31, 2003 FDA letter regarding the Agency's filing review of the nonprescription 20-mg PEPCID™ SNDA (S-015), a request was made for financial information of clinical investigators involved with studies 017 and 019. These studies were conducted in the late 1980s - early 1990s time period in support of the original PEPCID™ AC submission, prior to the February 2, 1998 effective date of the Final Rule on Financial Disclosure (21 CFR Part 54 and 314.50(k)).

Despite the fact that these studies predated the Final Rule and no investigator financial information was ever formally collected, Merck & Co., Inc. has acted with due diligence to search internal company databases and provide the following responses to the Agency's questions on investigator financial interests.

FDA Comment from Jan. 31, 2003 letter:

Because studies 017 and 019 were completed before the effective date of the Final Rule, the information required is limited to outcome payments and proprietary interests unless the studies were sponsored by a non-publicly traded company. In that case, information on equity interest must also be submitted.

Merck Response:

- Merck & Co., Inc., the sponsor of the studies in question, is a publicly traded company, and therefore equity interest information is not needed.
- With regard to outcome payments, Merck & Co., Inc. has an unequivocal policy of not entering into any financial arrangement with clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. In accordance with this policy, Merck & Co., Inc. has not entered into any financial arrangements with investigators from Protocols 017 and 019 whereby the value of the compensation could be affected by the outcome of the study (21 CFR 54.2(a)).
- With regard to proprietary interests, an internal search of the company's patent database has revealed that there are no U.S. patents that cover the formulation, composition, and/or method of use of the nonprescription 20-mg PEPCID™ product. Likewise, no patent rights connected with the product resulted from clinical investigator activity. In addition, a company search for any license or royalty obligation to third parties has revealed no licensing rights to any clinical investigators.



Mark I. Sildve, Senior Director
Worldwide Regulatory Operations

31 mar 2003

Date

54-6

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

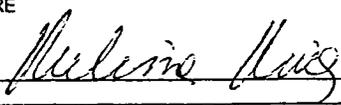
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Tables C-1 and C-2	
	Nonprescription Famotidine 20 mg	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Melissa King		TITLE Controller, MRL Financial Services	
FIRM/ORGANIZATION Merck & Co., Inc.			
SIGNATURE 		DATE 10/16/02	

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

**DISCLOSURE: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

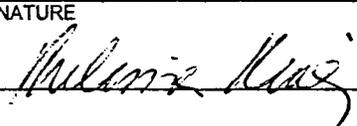
The following information concerning See Table D-1, who participated as a clinical investigator in the submitted study Nonprescription Famotidine 20 mg

Name of clinical investigator
clinical study
is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Melissa King	TITLE Controller, MRL Financial Services
FIRM/ORGANIZATION Merck & Co., Inc.	
SIGNATURE 	DATE 10/16/02

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Brenda A. McGuire, M.S., R.N.
Associate Director
Worldwide OTC Regulatory Affairs

Merck & Co., Inc.
BLX-29
P.O. Box 4
West Point PA 19486 USA
E-Mail: brenda_mcguire@merck.com
Tel 484 344 7235
Fax 484 344 3682

DESK COPY

March 26, 2003



Charles Ganley, M.D. Director
Division of Over-the-Counter Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Ganley:

**NDA 20-325/S-015: PEPCID™ AC Film Coated Tablets
(nonprescription famotidine 20 mg)**

Response to FDA Request for Information

(Commercial Marketing History)

Reference is made to the supplemental New Drug Application cited above for PEPCID™ AC submitted as an electronic archive on November 21, 2002 by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. and Johnson & Johnson ◦ Merck Consumer Pharmaceuticals Co., (JJCPC). This Prior Approval Supplement provides for a 20-mg PEPCID™ AC over-the-counter (OTC) product. Reference is also made to your letter dated January 31, 2003 and to the following issues for which the Agency has requested additional information:

Issue number 5

- Request tables showing countries where 10, 20, and 40mg tablets have been approved
- Date of approval, original and current marketing status (Prescription or over-the-counter (OTC), distinguishing between behind-the-counter vs. OTC)
- Approved indications
- Labeled duration of use

Issue number 6

- Request reasons for marketing application withdrawals

With this communication we are providing additional registration/marketing status information on the 10, 20, and 40-mg PEPCID™ products, as requested by the Medical Reviewer.

This amendment is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs*. As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one (1) Compact Disk (CD) which contains the amendment. All documents requiring signatures for certification are included as paper for archival purposes.

A list of reviewers from the Division of Over-the-Counter Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Mr. Dan Keravich, Regulatory Project Manager, Division of Over-the-Counter Drug Products.

All of the information is contained on one (1) CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 7.51, Symantec Corp., 2000) and we authorize the use of anti-virus software, as appropriate.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Brenda A. McGuire, M.S., R.N. (484-344-7235) or, in my absence, Edwin L. Hemwall, Ph.D. (484-344-2306).

Sincerely,



Brenda A. McGuire, M.S., R.N.
Associate Director
OTC Regulatory Affairs

Attachment
Enclosure: CD

Federal Express #1

Desk Copies: Mr. Dan Keravich
Regulatory Project Manager
HFD 560, CRP2, Room S214
Federal Express #2

Introduction

In the FDA letter of Jan. 31, 2003, the FDA requested additional marketing information with regard to 10-, 20- and 40-mg famotidine tablets. Specifically, the Reviewer has requested tables of the countries where these products have been approved, the date of approval, original and current marketing status (Rx or OTC, distinguishing between behind-the-counter and general sales), approved indications, and duration of use.

An explanation of our responses is provided below, with the requested tables following. It is important to note that, although an internal search for this information has been conducted, prescription PEPCID™ (famotidine) has been an approved, in-line product for Merck & Co., Inc., since 1986, and as such, has a vast worldwide registration history. Following patent expiration (early 2001), centralized marketing resources supporting the PEPCID™ franchise were discontinued, making retrieval of any current marketing information problematic. It is therefore possible that some of the information contained in these tables is no longer current (particularly details from the more remote locations worldwide). Whenever new information has been obtained, it has been included in the tables in an attempt to provide the most current information.

Additionally, it is important to note that Merck acquired marketing rights for famotidine from Yamanouchi (Japan) and may not be aware of other distribution sourced by non-Merck licensees. Finally, this listing does not attempt to capture marketing of famotidine by generic manufacturers in countries where the patent has expired or where intellectual property rights are not honored (e.g., India).

Famotidine 10-mg (FCT, Chewable tablets, Gelcaps, Famotidine/Antacid Combo)

Table 1 summarizes our knowledge of the registration experience for the 10-mg famotidine product worldwide. The famotidine/antacid combination products have been flagged with an “†”; all other products listed are single ingredient famotidine. Since the INTERNATIONAL PHYSICIANS CIRCULAR for PEPCIDINE™ (prescription famotidine) describes only 20- and 40-mg doses, it is assumed that all 10-mg approvals listed in Table 1 are for a nonprescription product. Likewise, it is assumed that the original and current registration status is the same unless indicated otherwise. It is not known whether all registered products were actually launched, however, wherever this information was made available it has been noted in the table.

The marketing status of nonprescription PEPCID™ 10 mg in several countries is classified as “behind-the-counter”, that is, the product is available without prescription but must be requested of the pharmacist. Those countries include France, Spain, Ireland, Italy, and Germany. To the best of our knowledge, all other 10-mg products listed in Table 1 are available to the consumer as a self-selection (general sales) product.

As stated in the PEPCID™ AC SUMMARY of PRODUCT CHARACTERISTICS (the approved worldwide labeling document) and the PEPCID™ AC PATIENT PRODUCT INFORMATION LEAFLET, the therapeutic indications for the 10-mg product are for:

- Treatment of:
 - Acid indigestion
 - Heartburn
 - Sour stomach
 - Symptoms of upset stomach associated with these conditions
- Prevention of these symptoms when associated with food and beverage

The duration of use is:

- No more than two tablets in a 24-hour period. Do not take continuously for more than two weeks except under the advice of a physician.

Some local variations in product indications (often translational differences) and duration of use may also apply.

Famotidine 20-mg and 40-mg Tablets

Table 2 summarizes our knowledge of the registration experience for the 20-mg famotidine product worldwide, and Table 3 summarizes the 40-mg experience.

To the best of our knowledge, all 20- and 40-mg famotidine products are available by prescription only, with the exception of 20-mg famotidine in Australia, which is both a prescription and over-the-counter product (Pepcidine M and Pepcid, respectively).

As stated in the PEPCID™ (prescription famotidine) PRODUCT CIRCULAR, and the PEPCIDINE™ (prescription famotidine) INTERNATIONAL PHYSICIANS CIRCULAR, the therapeutic indications for the 20- and 40- mg products are for:

- Treatment of duodenal ulcer
- Treatment of benign gastric ulcer
- Hypersecretory conditions such as Zollinger-Ellison Syndrome (ZES)
- Prevention of relapse of duodenal ulceration
- Prevention of relapse of benign gastric ulceration
- Symptomatic relief of gastroesophageal reflux disease (GERD)
- Healing of esophageal erosion or ulceration associated with GERD
- Prevention of relapse of symptoms and erosions or ulcerations associated with GERD

The duration of use varies according to the medical condition being treated and whether the product is being used for acute treatment or preventive maintenance. Treatment durations typically range from 4 weeks to indefinite time periods for maintenance therapy. Some local variations in product indications and duration of use may also apply.

Product Withdrawals

As noted in Table 4, three countries have deregistered (deleted, withdrawn) famotidine 10 mg (chewable tablets) from the market for reasons of ———— These countries include Finland, Norway and Sweden. No withdrawals occurred for any PEPCID™ product in any country for safety reasons.

Table 1
Countries Where Famotidine 10-mg Tablets (Film-coated, Chewable, and Gelcaps) and Famotidine 10 mg/Antacid Combination Tablets Have Received Marketing Approval

Country	Tradename	Dosage Form	Approval Date
Argentina	Effcid	FCT	May-1997
Argentina	Unknown	Chewable	May-1997
Australia	Pepcid	FCT	23-Jan-1996
Australia	Pepcid	Chewable	23-Jan-1996
Belgium	Pepcid AC	FCT	April-1996
Canada	Pepcid AC	FCT	14-Feb-1996 [†]
Canada	Pepcid AC Chewable	Chewable	14-Feb-1996 [†]
Canada	Pepcid AC Gelcap	Gelcap	Dec-1999 (not marketed)
Canada	Pepcid Plus [†]	Chewable	12-Jun-2000
	Pepcid Complete [†]	Chewable	19-Dec-2000 (name change)
Cyprus	Pepcid AC	FCT	24-Jun-1994
Finland	Pepcid	FCT	May-1996
Finland	Pepcid	Chewable	May-1996 (withdrawn May-2001)
Finland	PEPCID DUO [†]	Chewable	02-Sep-2000
France	Pepcid AC	FCT	21-Mar-1996
France	Pepcid AC	Chewable	21-Mar-1996 (not marketed)
France	PEPCIDDUO [†]	Chewable	22-Feb-2000
French Guiana	Pepcid AC	FCT	21-Mar-1996
French Guiana	Pepcid AC	Chewable	21-Mar-1996
French Polynesia	Pepcid AC	FCT	21-Mar-1996
French Polynesia	Pepcid AC	Chewable	21-Mar-1996
Germany	Pepcid akut	FCT	23-Dec-1997
Germany	Mylanta	FCT	23-Dec-1997 (not marketed)
Germany	PEPCIDDUAL [†]	Chewable	28-Mar-2001
Guadeloupe	Pepcid AC	FCT	21-Mar-1996
Guadeloupe	Pepcid AC	Chewable	21-Mar-1996
Hong Kong	Unknown	FCT	Jul-1995
Iceland	Pepcid AC	FCT	Oct-1995
Iceland	Pepcid AC	Chewable	Oct-1995
Ireland	Pepcid AC	FCT	Sep-1996
Ireland	Pepcid AC	Chewable	Sep-1996 (not marketed)
Ireland	PEPCIDTWO [†]	Chewable	29-Sep-2000
Italy	PEPCIDDUAL [†]	Chewable	05-Dec-2000
Japan	Gaster 10	FCT	Jul-1997
Malaysia	Pepcid AC	FCT	24-Dec-1998
Martinique	Pepcid AC	FCT	21-Mar-1996
Martinique	Pepcid AC	Chewable	21-Mar-1996

Table 1 (cont.)
Countries Where Famotidine 10-mg Tablets (Film-coated, Chewable, and Gelcaps) and Famotidine 10 mg/Antacid Combination Tablets Have Received Marketing Approval

Country	Tradename	Dosage Form	Approval Date
Mayotte	Pepcid AC	FCT	21-Mar-1996
Mayotte	Pepcid AC	Chewable	21-Mar-1996
Mexico	Pepcid AC	FCT	27-Jan-1995
Netherlands	Pepcidin AC	FCT	16-May-1995
Netherlands	Pepcidin AC	Chewable	16-May-1995 (not marketed)
New Caledonia	Pepcid AC	FCT	21-Mar-1996
New Caledonia	Pepcid AC	Chewable	21-Mar-1996
New Zealand	Pepcid AC	FCT	08-Sep-1994
New Zealand	Pepcid AC	Chewable	17-Apr-1997
Norway	Pepcid AC	FCT	Jan-1997
Norway	Pepcid AC	Chewable	Oct-1997 (withdrawn Mar-2000)
Norway	PEPCID DUO [†]	Chewable	11-Jan-2001
Reunion	Pepcid AC	FCT	21-Mar-1996
Reunion	Pepcid AC	Chewable	21-Mar-1996
Singapore	Pepcid AC	FCT	29-Mar-1996
Spain	PEPCID	FCT	13-May-1998
Spain	PEPCID	Chewable	02-Aug-2001 (not marketed)
Spain	PEPDUAL [†]	Chewable	03-Aug-2001
Sweden	Pepcid AC	FCT	Mar-1995
Sweden	Pepcid	Chewable	Mar-1995 (withdrawn Jun-2000)
Sweden	PEPCID DUO [†]	Chewable	23-Mar-2001
Switzerland	Pepcid AC	FCT	13-Dec-1996
Switzerland	Pepcid AC	Chewable	13-Dec-1996
United Kingdom	Pepcid AC/Boots Excess Acid Control [§]	FCT	04-Feb-1994
United Kingdom	Pepcid AC Chewable	Chewable	02-Apr-1996 (not marketed)
United Kingdom	PEPCIDTWO ^{†§}	Chewable	15-May-2001
United States	Pepcid AC	FCT	28-Apr-1995
United States	Pepcid AC	Chewable	24-Sep-1998
United States	Pepcid AC	Gelcap	05-Aug-1999
United States	Pepcid Complete [†]	Chewable	16-Oct-2000

[†] Famotidine 10 mg/antacid combination product.

[‡] Nonprescription status in Canada varies (general sales or behind-the-counter sales) by Province.

[§] Originally approved for behind-the-counter sales, and subsequently switched to general sales status.

Note: All 10-mg products have a nonprescription sales status. Most are self-selection (general sales), however, the 10-mg PEPCID product is sold "behind-the-counter" (i.e., must be requested of pharmacist) in France, Spain, Ireland, Italy and Germany.

Table 2
Countries Where Famotidine 20-mg Tablets Have Received Marketing Approval

Country	Tradename	Approval Date
Armenia	Pepcidine	02-Oct-1994
Australia	Pepcid	01-Jul-1988
Australia	Pepcidine M	01-Jul-1988
Bahrain	Pepcidin	05-Nov-1988
Belgium	Pepcidine	02-Mar-1988
Benin	Pepdine	14-Mar-1987
Cameroon	Pepdine	26-Oct-1988
Canada	Pepcid	07-Oct-1986
Central African Republic	Pepdine	05-Mar-1995
Congo	Pepdine	12-Aug-1988
Costa Rica	Pepcid	09-Sep-1997
Cyprus	Pepcidin	13-Mar-1987
Denmark	Pepcidin	03-Dec-1986
El Salvador	Pepcidine	25-Sep-1998
Finland	Pepcidin	08-Jul-1987
France	Pepdine	03-Mar-1987
French Guiana	Pepdine	03-Mar-1987
French Polynesia	Pepdine	03-Mar-1987
Gabon	Pepdine	11-Nov-1988
Germany	Pepdul 20 mg	20-Dec-1995
Germany	Pepdul Mite	05-Aug-1985
Ghana	Pepdine	29-May-1992
Greece	Peptan	08-Apr-1986
Guadeloupe	Pepdine	03-Mar-1987
Guatemala	Pepcidine	03-Feb-1998
Guinea	Pepdine	03-Nov-1992
Honduras	Pepcidine	21-Jan-1999
Hong Kong	Pepcidine	13-Jan-1988
Ireland	Pepcid	06-Oct-1987
Italy	Gastridin 20	10-Jul-1985
Ivory Coast	Pepdine	11-Mar-1988
Jordan	Pepcidin	01-Jan-1988
Kenya	Pepdine	24-Nov-1989
Kuwait	Pepcidin	01-Aug-1988
Lebanon	Pepcidin	01-Dec-1988
Luxembourg	Pepcidine	05-Jul-1988
Malaysia	Pepcidine	07-Sep-1990
Mali	Pepdine	06-Jun-1992
Martinique	Pepdine	03-Mar-1987
Mauritania	Pepdine	20-Feb-1989
Mauritius	Pepdine	08-May-1989
Mayotte	Pepdine	03-Mar-1987

Table 2
Countries Where Famotidine 20-mg Tablets Have Received Marketing Approval

Country	Tradename	Approval Date
Mexico	Pepcidine	26-Aug-1986
Netherlands	Pepcidin	02-Feb-1987
New Caledonia	Pepdine	03-Mar-1987
New Zealand	Pepcidine M	28-Aug-1986
Nicaragua	Pepcidine	30-Jun-1998
Niger	Pepdine	29-Jan-1993
Norway	Pepcidin	28-Sep-1989
Oman	Pepcidin	01-Jun-1989
Panama	Pepcidine	27-Jan-1999
Philippines	Pepcidine	14-Aug-1996
Portugal	Pepcidina	04-Dec-1985
Qatar	Pepcid	01-Nov-1987
Reunion	Pepdine	03-Mar-1987
Saudi Arabia	Pepcidin	13-Oct-1988
Senegal	Pepdine	28-May-1990
Singapore	Pepcidine	03-Oct-1988
Slovakia	Pepcidine	24-Jun-1997
South Africa	Pepcid	11-Jan-1989
Spain	Tamin	09-Jul-1987
Sweden	Pepcidin	27-Mar-1987
Switzerland	Pepcidine	14-Jun-1985
Thailand	Pepcidine	28-May-1990
Togo	Pepdine	10-Mar-1988
United Arab Emirates	Pepcidin	01-Jun-1988
United Kingdom	Pepcid	08-Sep-1987
United States	Pepcid	15-Oct-1986
Venezuela	Pepcidine	29-Jan-1997
Vietnam	Pepcidine	02-Dec-1995

Note: All 20-mg products have a prescription sales status except for OTC Pepcid 20-mg in Australia. There have been no withdrawals of any of the 20-mg products due to safety reasons.

**APPEARS THIS WAY
ON ORIGINAL**

Table 3
Countries Where Famotidine 40-mg Tablets Have Received Marketing Approval

Country	Tradename	Approval Date
Argentina	Pepcidine	20-Mar-1987
Armenia	Pepcidine	02-Oct-1994
Aruba	Pepcid	08-Jun-1994
Australia	Amfamox	07-Jan-1994
Australia	Pepcidine	01-Jul-1988
Bahrain	Pepcidin	27-Oct-1988
Belgium	Pepcidine	02-Mar-1988
Benin	Pepdine	14-Mar-1989
Bolivia	Pepcidine	11-Sep-1991
Cameroon	Pepdine	26-Oct-1988
Canada	Pepcid	07-Oct-1986
Central African Republic	Pepdine	05-Mar-1995
Colombia	Pepcidine	18-Feb-1986
Congo	Pepdine	12-Aug-1988
Costa Rica	Pepcid	14-Aug-1986
Curacao	Pepcid	22-Dec-1992
Cyprus	Pepcidin	13-Mar-1987
Denmark	Pepcidin	03-Dec-1986
Dominican Republic	Pepcid	13-Dec-1993
El Salvador	Pepcidine	20-May-1987
Finland	Pepcidin	08-Jul-1987
France	Pepdine	03-Mar-1987
French Guiana	Pepdine	03-Mar-1987
French Polynesia	Pepdine	03-Mar-1987
Gabon	Pepdine	11-Nov-1988
Germany	Pepdul 40 mg	20-Dec-1995
Germany	Pepdul	05-Aug-1985
Ghana	Pepdine	29-May-1992
Greece	Peptan	08-Apr-1986
Guadeloupe	Pepdine	03-Mar-1987
Guatemala	Pepcidine	26-May-1987
Honduras	Pepcidine	20-May-1987
Hong Kong	Pepcidine	13-Jan-1988
Ireland	Pepcid	06-Oct-1987
Italy	Motiax Compresse	28-Sep-1985
Ivory Coast	Pepdine	11-Mar-1988
Jamaica	Pepcid	09-Feb-2001

Table 3 (cont.)
Countries Where Famotidine 40-mg Tablets Have Received Marketing Approval

Country	Tradename	Approval Date
Jordan	Pepcidin	01-Jan-1988
Kenya	Pepdine	24-Nov-1989
Kuwait	Pepcidin	01-Aug-1988
Lebanon	Pepcidin	17-Sep-1997
Luxembourg	Pepcidine	05-Jul-1988
Malaysia	Pepcidine	07-Sep-1990
Mali	Pepdine	01-Jan-1988
Martinique	Pepdine	03-Mar-1987
Mauritania	Pepdine	22-Feb-1989
Mauritius	Pepdine	08-May-1989
Mayotte	Pepdine	03-Mar-1987
Mexico	Pepcidine	26-Aug-1986
Netherlands	Pepcidin	02-Feb-1987
New Caledonia	Pepdine	03-Mar-1987
New Zealand	Pepcidine	28-Aug-1986
Nicaragua	Pepcidine	01-Jul-1990
Niger	Pepdine	29-Jan-1993
Norway	Pepcidin	28-Sep-1989
Oman	Pepcidin	01-Jun-1989
Pakistan	Pepcidine	21-Apr-1988
Panama	Pepcidine	01-Apr-1988
Peru	Pepcidine	08-Apr-1993
Philippines	Pepcidine	31-Jul-1992
Portugal	Pepcidina	04-Dec-1985
Qatar	Pepcidin	01-Nov-1987
Reunion	Pepdine	03-Mar-1987
Saudi Arabia	Pepcidin	24-Jan-1990
Senegal	Pepdine	28-May-1990
Singapore	Pepcidine	03-Oct-1988
Slovakia	Pepcidine	24-Jun-1997
South Africa	Pepcid	11-Jan-1989
Spain	Tamin 40 mg	09-Jul-1987
Sri Lanka	Pepcidine	13-Dec-1993
Sweden	Pepcidin	27-Mar-1987
Switzerland	Pepcidine	14-Jun-1985
Thailand	Pepcidine	28-May-1990
Togo	Pepdine	10-Mar-1988
Trinidad	Pepcid	19-Apr-1989
United Arab Emirates	Pepcidin	05-Oct-1990

Table 3 (cont.)
Countries Where Famotidine 40-mg Tablets Have Received Marketing Approval

Country	Tradename	Approval Date
United Kingdom	Pepcid PM	08-Sep-1987
United Kingdom	Pepcid 40 mg Tablets	08-Sep-1987
United States	Pepcid	15-Oct-1986
Venezuela	Pepcidine	29-Jan-1997
Vietnam	Pepcidine	02-Dec-1995

Note: All 40-mg products have a prescription sales status. There have been no withdrawals of any of the 40-mg products due to safety reasons.

Table 4
Countries Where Applications for Famotidine Have Been Withdrawn by Merck

Country	Tradename	Dosage	Type	Approval Date	Deregistered/ Withdrawal Date
Finland	Pepcid	10 mg	Chewable	May-1996	13-May-2001 [§]
Norway	Pepcid AC	10 mg	Chewable	14-Oct-1997	01-Mar-2000 [§]
Sweden	Pepcid	10 mg	Chewable	09-Mar-1995	30-Jun-2000 [§]

[§] Product was deregistered for business reasons ————— There have been no withdrawals of any 10-, 20- or 40-mg Pepcid products due to safety reasons.

**APPEARS THIS WAY
ON ORIGINAL**

SC-2-015-C

Brenda A. McGuire, M.S., R.N.
Associate Director
Worldwide OTC Regulatory Affairs

Merck & Co., Inc.
BLX-29
P.O. Box 4
West Point PA 19486 USA
E-Mail: brenda_mcguire@merck.com
Tel 484 344 7235
Fax 484 344 3682

February 14, 2003

DUPLICATE

Charles Ganley, M.D. Director
Division of Over-the-Counter Drug Products

RECEIVED



MERCK
Research Laboratories
RECEIVED

FEB 20 2003

FEB 19 2003

MEGA/CDER

CDR/CDER

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

SC-2-015/NC
SUPPL NEW CORRESP

Dear Dr. Ganley:

**NDA 20-325/S-015: PEPCID™ AC Film Coated Tablets
(nonprescription famotidine 20 mg)**

**Response to FDA Request for Information
(Patent Information)**

Reference is made to the supplemental New Drug Application cited above for PEPCID™ AC submitted as an electronic archive on November 21, 2002 by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. and Johnson & Johnson ◦ Merck Consumer Pharmaceuticals Co., (JJCPC). This Prior Approval Supplement provides for a 20 mg PEPCID™ AC over-the-counter (OTC) product. Reference is also made to your letter dated January 31, 2003, issue number 3, requesting the location in the electronic records or the submission of the necessary information for patents that is required in 314.50(h) and 314.53.

With this communication we are providing Patent and Exclusivity Information for this nonprescription famotidine 20 mg application. As indicated in the attachment, there are no U.S. patents that cover the formulation, composition, and/or method of use of the product. However, 3 years of exclusivity is being sought in accordance with Hatch-Waxman guidelines, pending FDA agreement that clinical studies that have been conducted by the sponsor are essential to support the approval of the application. We hope this response adequately addresses the Agency's request for patent information.

This amendment is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry - Providing Regulatory Submissions in Electronic Format - NDAs*. As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one (1) Compact Disk (CD) which contains the amendment. All documents requiring signatures for certification are included as paper for archival purposes.

A list of reviewers from the Division of Over-the-Counter Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Mr. Dan Keravich, Regulatory Project Manager, Division of Over-the-Counter Drug Products.

All of the information is contained on one (1) CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 7.51, Symantec Corp., 2000) and we authorize the use of anti-virus software, as appropriate.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Brenda A. McGuire, M.S., R.N. (484-344-7235) or, in my absence, Edwin L. Hemwall, Ph.D. (484-344-2306).

Sincerely,



Brenda A. McGuire, M.S., R.N.
Associate Director
OTC Regulatory Affairs

Attachment
Enclosure: CD

Federal Express #1

Desk Copies: Mr. Dan Keravich
Regulatory Project Manager
HFD 560, CRP2, Room S214
Federal Express #2

Maryann Holovac (cover letter and patent)
Orange Book Staff
Office of Generic Drugs
HFD-610, Room 134
7500 Standish Place
Rockville, MD 20855-2773
Federal Express #3



FILING ISSUES IDENTIFIED

NDA 20-325/S-015

Merck & Co., Inc.
Attention: Brenda McGuire, M.S., R.N.
Regulatory Affairs
Sumneytown Pike, P.O. Box 4, BLX-29
West Point, PA 19486

Dear Ms. McGuire:

Please refer to your November 22, 2002, supplemental new drug application (SNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pepcid (famotidine) Tablet.

We also refer to your submission dated December 13, 2002.

We have completed our filing review of your application and have identified the following issues.

1. As required by 21 CFR Part 54 and 314.50(k), before this application may be approved, financial disclosure information must be submitted for studies 017 and 019. Because these studies were completed before the effective date of the final rule, the information required is limited to outcome payments and proprietary interests unless the studies were sponsored by a non-publicly traded company. In that case, information on equity interest must also be submitted. We note that the December 31, 1998, amendment to the final rule on financial disclosure specifically declined to revise the requirements for collection of information under 21 CFR 54.2(a) and 54.2(c), and under 21 CFR 54.2(b) for any ownership interest whose value cannot be readily determined through reference to public prices, for studies supporting applications submitted after February 1, 1999 (63 FR 72173). If this information cannot be provided, you must submit a certification that you acted diligently to obtain the information but were unable to do so and include the reason why such information could not be obtained. We note that the required information should be known by Merck (or the study sponsor) and, therefore, does not require clinical investigator disclosure.
2. We were unable to locate Study 137 in the electronic submission. Study 137 was not included under the STATS folder. Also, the Program Documentation and User Guide for Statistical Reviewing Aid for Study 137 was missing. Please provide the location in the submission, or provide the study information in electronic format, along with the Program Documentation and User Guide for Statistical Reviewing Aid for Study 137.

3. Patent information was not located in your submission. Please provide the location in the electronic records or submit the necessary information for patents that is required in 314.50(h) and 314.53.
4. On initial review, the labeling for the proposed 20mg product formulation was inconsistent with the labeling for the currently approved 10mg formulation. Drug Facts contents and formatting issues were identified. We will forward to you a complete set of comments from the review of the proposed labeling later in the review cycle. In addition, please submit the Drug Facts specifications (e.g., type and bullet sizes etc.) in accordance with 21 CFR 201.66(d).
5. Provide tables showing countries where 10, 20 and 40 mg tablets have been approved, the date of approval, original and current marketing status [Rx or OTC (distinguish behind the counter vs. OTC as in the US)], approved indications, and labeled duration of use.
6. If a marketing application was withdrawn by Merck either before or after approval in any country, provide the reason why this was done.
7. Provide narrative summaries from worldwide postmarketing surveillance of serious adverse events involving the hematologic, hepatic, nervous (including psychiatric disorders), and renal systems. These summaries should be separated by dose.
8. If possible, please provide a tabular summary of the literature references in a form that could be edited.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

If you have any questions, call Dan Keravich, R.Ph., M.Sc., M.B.A., Regulatory Project Manager, at (301) 827-2248.

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Charles Ganley
1/31/03 04:29:13 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-325/S-015

Merck & Co., Inc.
Brenda McGuire, M.S., R.N.
Regulatory Affairs
Sunneytown Pike, P.O. Box 4, BLX-29
West Point, PA 19486

Dear Ms. McGuire:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Pepcid AC ® 20mg (famotidine) Tablet

NDA Number: 20-325

Supplement number: 015

Review Priority Classification: Standard

Date of supplement: November 22, 2002

Date of receipt: November 22, 2002

This supplemental application proposes a new 20mg tablet for the prevention and treatment of heartburn.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 21, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 22, 2003.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Over-the Counter Drug Products, HFD-560
Attention: Document Control Room
5600 Fishers Lane (HFD-560)
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and research
Division of Over-the Counter Drug Products, HFD-560
Attention: Document Room
9201 Corporate Boulevard, HFD560
Rockville, Maryland 20850

If you have any question, call Daniel P. Keravich, R.Ph., M.Sc., M.B.A., Regulatory Health Project Manager, at 301-827-2248.

Sincerely,

{See appended electronic signature page}

David Hilfiker
Chief, Project Management Staff
Division of Office of Drug Evaluation V
Division of Over-the Counter Drug Products
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

David Hilfiker
1/8/03 10:52:58 AM

Brenda A. McGuire, M.S., R.N.
Associate Director
Worldwide OTC Regulatory Affairs

Merck & Co., Inc.
BLX-29
P.O. Box 4
West Point PA 19486 USA
E-Mail: brenda_mcguire@merck.com
Tel 484 344 7235
Fax 484 344 3682

November 22, 2002

Charles Ganley, M.D., Director
Division of Over-the-Counter Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852



RECEIVED

NOV 22 2002

CDR/CDER

RECEIVED

NOV 26 2002

MEGA/CDER

Dear Dr. Ganley:

NDA 20-325: PEPCID™ AC Film Coated Tablets NDA NO. 20-325 REF NO. 015
(nonprescription famotidine) NDA SUPPL FOR SE8

**Prior Approval Supplement
(nonprescription famotidine 20 mg)**

User Fee ID No. 4454

Reference is made to the New Drug Application noted above, and to meetings held on December 10, 1997, December 16, 1998, August 7, 2001, May 30, 2002 and June 20, 2002, between Merck Research Laboratories (MRL), a Division of Merck and Co., Inc., Johnson & Johnson • Merck Consumer Pharmaceuticals Co. (JJCPC), and representatives of the FDA Divisions of Gastrointestinal and Coagulation Drug Products, Over-The-Counter (OTC) Drug Products, Biometrics II, and New Drug Chemistry III, to discuss the requirements of a clinical development program that would support the approval of a 20-mg nonprescription PEPCID™ product. Reference is also made to a written communication of August 20, 2002, in which a summary of the sources of efficacy and safety data to be included in this sNDA was provided to FDA.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in the Labeling, Chemistry, Manufacturing and Controls, and Clinical and Statistical Sections of the approved New Drug Application for PEPCID™ AC Film Coated Tablets, in support of a 20-mg nonprescription famotidine product. The manufacturing site, Merck Manufacturing Division, West Point, PA, and the packaging sites, _____ Johnson & Johnson-Merck Consumer Pharmaceuticals Company, Lancaster, PA, and _____ are prepared for a Pre-Approval Inspection (PAI) in connection with this supplemental NDA.

The Statement of Organization following this letter describes the sections contained in this application.

DUPLICATE

Merck & Co., Inc. is requesting a categorical exclusion for the requirements to prepare an Environmental Assessment under 21 CFR 25.31(b). This production of famotidine meets the requirements of a categorical exclusion under 21 CFR 25.31(b), because the estimated concentration of the drug substance for all images at the point of entry into the aquatic environment (referred to as the Expected Introduction Concentration (EIC)), will be below 1 part per billion (ppb). To Merck's best knowledge, no extraordinary circumstance exists in regard to this action.

In accordance with the Prescription Drug User Fee Act of 1992 (PDUFA) and reauthorized in the Food and Drug Administration Modernization Act of 1997 (FDAMA), and the Prescription Drug User Fee Amendments of 2002 (PDUFA III) a check (Check No. _____, in the amount of \$266,700, was sent to the Food and Drug Administration ←_____ Mellon Client Services, Center RM 670, 500 Ross Street, Pittsburgh, PA on November 12, 2002. The User Fee I.D. number is 4454.

A list of reviewers from the Division of Over-the-Counter Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Dr. Walter Ellenberg, Regulatory Project Manager, Division of Over-the-Counter Drug Products.

We consider the filing of this supplemental New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Brenda A. McGuire, M.S., R.N. (484-344-7235) or, in my absence, Edwin L. Hemwall, Ph.D. (484-344-2306).

Sincerely,



Brenda A. McGuire, M.S., R.N.
Associate Director
Worldwide OTC Regulatory Affairs

Enclosure: CD
Federal Express #1

Desk Copies: Dr. Walter Ellenberg, Regulatory Project Manager (cover letter)
HFD 560, Room S214
Federal Express #2

Ms. Debra L. Pagano, Philadelphia District Office, FDA
Federal Express #3

STATEMENT OF ORGANIZATION

**NDA 20-325: PEPCID™ AC Film Coated Tablets
(Nonprescription Famotidine)**

**Supplemental New Drug Application
(nonprescription famotidine 20 mg)**

This submission contains the following paper and/or electronic information:

<u>ITEM(s)</u>	<u>DESCRIPTION</u>	<u>Contents on Archival CD</u>	<u>Archival Copy</u>	<u>Paper Review Copies</u>
1,16,17,18,19,20	Administrative Data containing Archival CD	Yes	Blue Binder (1 volume)	Red Binder, Orange Binder, Green Binder, Tan Binder (1 volume each)
2	Labeling	Yes	No	
3	Synopsis of Application	Yes	No	
4	Chemical and Pharmaceutical Manufacturing and Controls Documentation	Yes	No	Red Binder (3 volume)
6	Human Pharmacology and Bioavailability/Bioequivalence Documentation	Yes	No	Orange Binder (1 volume)
8,10	Clinical and Statistical Documentation	Yes SAS Dataset as .xpt and SAS programs as .sas are located in the CRT folder.	No	Tan Binder (3 volume) Green Binder (3 volume)
11	Case Report Tabulations	Yes (SAS transport files)	No	No
12	Case Report Forms	Yes	No	No

TOTAL VOLUMES: 15

NDA 20-325
Nonprescription Famotidine 20 mg

ATTACHMENT to 356H
NDA 20-325: Nonprescription PEPCID™ AC
(famotidine)

MANUFACTURING SITES LISTED IN THE NDA

<u>Drug Product</u>
<p><u>Formulation and Manufacturing:</u></p> <p>Maria Wirths Director Pharmaceutical GMP Compliance Merck & Co., Inc. 770 Sumneytown Pike West Point, PA 19486-0004 CFN - 2510592 215- 652-3540</p> <p><u>Labeling and Packaging:</u></p> <div data-bbox="459 951 865 1228"></div> <p>Glenn Marina Plant Manager Johnson & Johnson-Merck Consumer Pharmaceuticals Company 1838 Colonial Village Lane Lancaster, PA 17601 CFN - 2529821 717-207-3528</p> <div data-bbox="448 1516 883 1753"></div>

All manufacturing and packaging facilities listed in this supplement are prepared to support a pre-approval inspection.

11/22/02 MERCK LETTER

Redacted _____

Page(s) of trade

secret and /or

confidential

commercial

information