

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-325 / S-015

MEDICAL REVIEW

OTC Medical Team Leader's Secondary Review

NDA 20-325/Supplement 015

Drug Name: Pepcid 20 mg

Sponsor: Merck & Co., Inc.

Pharmacologic Category: H2 Receptor Antagonist

Proposed Indication: Prevention and Relief of Occasional Heartburn

Dosage Form/Route of Administration: Tablet/Oral

Submission Date: 11/22/02

Review Date: 9/3/03

Reviewer Name: Andrea Leonard-Segal, M.D., M.S.

Background:

The sponsor has submitted an application to switch the prescription strength Pepcid 20 mg tablet from prescription to OTC status for up to twice daily use. The OTC Pepcid 20 mg tablet would have the same heartburn relief and prevention indications as the currently available Pepcid AC 10 mg OTC tablet. Dr. Linda Hu, the DOTCP primary medical reviewer, has completed a detailed safety review that considers the data provided by 8 clinical trials (P114, P117, P118, P119, P128, P137, P017, P019), postmarketing adverse event reports, and literature published between the period of 31-May-1992 through 30-June-2002. That review is available in the electronic Divisional Files System.

Adverse Events:

In the 8 clinical trials Pepcid 20 mg was associated with mild, non-serious side effects (i.e., headache, dizziness, diarrhea, constipation) that have been previously reported in association with Pepcid use.

The postmarketing reports revealed approximately twice the number of serious adverse events and deaths at the 40 mg daily dose than at the currently available 20 mg OTC daily dose. This was the case for serious adverse events even when the subjects were outpatients and when the drug was used for 14 days or less. Although the reported cases were often confounded, it is still possible that famotidine was related to many of the adverse events. The prescription labeling "Adverse Reactions" section for Pepcid is consistent with most of the reported events.

Published literature reports support the prescription Pepcid label recommendation that a dosage reduction be made for patients with renal insufficiency. See Dr. Hu's review for details.

Conclusion:

It is of concern that the availability of the Pepcid 20 mg tablet for BID use OTC may increase the risk of serious adverse events for the consumer. This is particularly an issue because of the lack of seriousness of the condition for which Pepcid 20 mg tablets would be indicated and the multitude of products already available to treat that condition OTC.

Recommendations:

I agree with the recommendations in Dr. Hu's review that the application not be approved. If it is approved, I also agree with her recommendation that the label include a warning for ~~_____~~

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/s/

Andrea Segal
9/5/03 09:40:45 AM
MEDICAL OFFICER

**Pepcid 20 mg Tablet
OTC Switch**

NDA 20-325/Supplement - 015

Medical Safety Review

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**APPEARS THIS WAY
ON ORIGINAL**

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Approval of the present application is not recommended. The safety data from clinical trials submitted in this application establish only that the frequency of common side effects (such as headache, constipation, diarrhea, and dizziness) is similar for famotidine 20 mg and famotidine 10 mg. However, available post-marketing surveillance and marketing data indicate increased numbers of serious adverse events and deaths at the higher 40 mg daily dose when compared to the 20 mg daily dose that is currently available OTC. Although the risks of serious events are low, the available information does not establish a favorable risk-benefit ratio for OTC approval of the higher strength formulation, since the medication provides only symptomatic relief for a condition which is not life-threatening and for which other treatment options are available. Other drugs currently available OTC in the US with heartburn indications include: other H₂ blockers, antacids, and a proton pump inhibitor. Since the public already has several options in the OTC marketplace, this reviewer does not find it in the public's interest to switch the higher 20 mg strength tablet to be used up to twice daily from prescription to OTC status.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps If Approvable

If a 20 mg famotidine oral tablet formulation is approved OTC, a _____ would be advisable; see Executive Summary, Section II.D.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

This is a clinical review focused on the safety of famotidine 20 mg tablets for over-the-counter (OTC) use. The efficacy review is being conducted by HFD-180. The product name is MAXIMUM STRENGTH Pepcid AC, and it will be labeled for the relief and prevention of heartburn associated with acid indigestion and sour stomach in those aged 12 and above. The product use directions will state that no more than two tablets should be taken in a 24-hour period and that consumers should not take the product continuously for more than two weeks except under the advice of a physician.

The clinical program for this application consisted of the following trials:

- One pharmacodynamics study (P118, N=24 subjects) to compare the gastric antisecretory activity of 10 mg versus 20 mg of famotidine, given 10 minutes prior to a provocative evening meal.

- Four trials supporting a prevention indication, study protocol numbers P114, P117, P128, P137; the total number of subjects exposed to famotidine 20 mg in these four trials was N=1425.
- One multiple dose pattern of use study P119, with N=523 subjects.
- Two trials supporting a relief indication, study protocol numbers P017 and P019; the total number of subjects exposed to famotidine 20 mg in these two trials was N=245.

The combined total of subjects in the clinical program receiving famotidine 20 mg for the prevention and relief of heartburn was N=2217.

B. Efficacy

Please refer to review by HFD-180.

C. Safety

The safety database submitted in support of this OTC switch application included four trials for a prevention indication, a pharmacodynamics study, a use trial, and another two trials for a relief indication. In the prevention clinical trials, the use trial, and the pharmacodynamics trial, the total number of patients exposed to famotidine 20 mg was 1972. Of these, 1306 (66%) took single doses in controlled studies, and another 143 (7.3%) took four doses in the controlled study P137. In the use study P119, a total of 523 subjects took the medication over a 3 week period. In the heartburn relief trials, there were another 245 patients exposed to the 20 mg tablets over a period of 4 weeks.

The present review will discuss over 492 serious adverse event reports from world-wide post marketing surveillance of famotidine, in the following body systems: hematologic and lymphatic, hepatobiliary, nervous system and psychiatric, and renal and urinary systems. Famotidine is a widely used medications in the US and world-wide. The Sponsor stated that in the US since 1995, over ~~————~~ famotidine 10 mg tablets have been sold OTC.

However, Australia is the only country in which 20 mg famotidine tablets are currently available OTC. Experience with the higher strength tablet marketed OTC is therefore limited.

According to the drug insert, common adverse reactions include the following, reported in more than 1% of patients in controlled clinical trials: headache (4.7%), dizziness (1.3%), constipation (1.2%) and diarrhea (1.7%). The following additional adverse reactions have been reported infrequently in clinical trials or post-marketing reports. The relationship to therapy with famotidine has been unclear in many cases. Within each category the adverse reactions are listed in order of decreasing severity:

Cardiovascular: arrhythmia, AV block, palpitation

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

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

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

Musculoskeletal: musculoskeletal pain including muscle cramps, arthralgia

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

Respiratory: bronchospasm

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

Special Senses: tinnitus, taste disorder

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

The present reviewer notes that the following rare adverse events were retrieved from the literature and/or post-marketing surveillance reports, but are not listed in the prescription labeling information for famotidine:

aplastic anemia, ITP, TTP, QT prolongation, rhabdomyolysis, hepatic necrosis, hepatic failure, hepatitis, mixed hepatocellular jaundice, pancreatitis, carcinoid tumor

The relationship to therapy may be unclear. This information will be shared with HFD-180 for further consideration.

D. Dosing

Available information from the literature supports the current prescription famotidine labeling information that recommends dosage reduction by one half for patients with moderate or severe renal insufficiency (defined as creatinine clearance <50 mL/min). If the higher strength oral famotidine formulation is approved OTC, some means would be required to implement a dose reduction in patients with impaired renal function. The Sponsor has agreed to include a label warning stating that patients with kidney disease should ask a doctor before use.

However, many elderly people have silent renal insufficiency and may not be aware, or have never been told by their doctors, that they have reduced renal function. Many elderly OTC consumers may misunderstand a "kidney disease" warning because they think that the warning would not apply to them. Even if they have been told that their kidneys are not functioning as well as they used to, they may assume that it is a result of aging and not a "disease".

In elderly patients the creatinine clearance can be overestimated from BUN and creatinine values, because of decreased muscle mass. Further, creatinine clearance values will often not be available. An alternative method is needed to guide OTC consumers, using a surrogate marker that is easily understood, generally available, and reasonably well correlated with creatinine clearance. For famotidine, age is the obvious marker. If the product were available OTC at the 20 mg strength,

This direction would protect many OTC famotidine users, because the median age of these consumers is estimated as 50 from the actual use trial submitted for this application, and because the serious adverse events involving famotidine occur more frequently in older patients.

Unresolved Safety Issue. The safety data from clinical trials submitted in this application establish only that the frequency of common side effects (such as headache,

constipation, diarrhea, and dizziness) is similar for famotidine 20 mg and famotidine 10 mg. However, available post-marketing surveillance and marketing data indicate increased numbers of serious adverse events and deaths at the higher 40 mg daily dose when compared to the 20 mg daily dose that is currently available OTC. The available data are not adequate to determine whether a dose response exists. Although the risks of serious events are low, the available information does not establish a favorable risk-benefit ratio for OTC approval of the higher strength formulation, since the medication provides only symptomatic relief for a condition that is not life-threatening and for which other OTC options are available.

E. Special Populations

If approved, _____

This proposed OTC product is not labeled for use in those under 12 years of age. There have been no studies of heartburn prevention or relief in subjects between the ages of 12 and 18. The prescription labeling however allows for dosing in children up to 16 years of age for Gastroesophageal Reflux Disease (GERD) with or without erosions and ulcerations as follows: 1.0 mg/kg/day p.o. divided b.i.d., up to a maximum of 40 mg b.i.d. It mentions that published uncontrolled clinical studies in pediatric patients have employed doses up to 2 mg/kg/day for GERD with or without esophagitis including erosions and ulcerations. However, only the lower dose of 1 mg/kg/day is recommended for GERD, and no clinical trial data are available for heartburn in children. If the 20 mg famotidine tablet were made available OTC and were used in children, then the two tablet per day dose would exceed the recommended dose for children who are under 40 kgs.

The product is labeled as Pregnancy Category B.

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Clinical Review

I. Introduction and Background

This is a clinical review focused on the safety of famotidine 20 mg b.i.d. for over-the-counter (OTC) use. The efficacy review is being done by Dr. Lopez (HFD-180).

A. Drug Name and Indications

This is an OTC switch application for famotidine 20 mg (MAXIMUM STRENGTH Pepcid AC) for the relief and prevention of heartburn associated with acid indigestion and sour stomach in those aged 12 and above. The therapeutic indications are as follows:

- 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

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.

B. OTC Armamentarium

Other H2 blockers available OTC for these relief and prevention indications include ranitidine, cimetidine, and nizatidine. Antacids are also available OTC for heartburn. A proton pump inhibitor (omeprazole) has been approved for OTC use to treat frequent heartburn.

C. Important Milestones in Product Development

On December 10, 1997, December 16, 1998, and August 7, 2001, sponsor representatives met with 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 obtain Agency advice on the 20 mg OTC clinical development program, specifically with regard to target populations, indications and extent of clinical studies required for approval. At these early meetings, the Sponsor was advised that a distinct OTC population or a distinct indication was needed that would distinguish a 20 mg product from the current 10 mg PEPCID™ AC product. Relief and prevention of heartburn indications could be evaluated independently of one another, and the proposed 20 mg OTC product could be approved for either or both indications. Safety information from the original PEPCID™ AC NDA 20-325 studies could be included to support safety. Based on this advice, a clinical program was developed that focused on a 20 mg PEPCID™ product for heartburn prevention.

The Agency reconsidered its position that the indication or target population for famotidine 20 mg must be distinct from that for famotidine 10 mg. Thus, at a May 30, 2002 meeting between the Sponsor and members of the FDA Divisions of GI and Coagulation Drug Products and Over-the-Counter Drug Products, it was established that

a general population would be an appropriate target population for the prevention or relief of heartburn with PEPCID™ OTC 20 mg. In addition, the Agency encouraged the development of both relief and prevention indications in order to make the 20 mg label more analogous to the currently approved PEPCID™ AC 10 mg product label. In this case, no further label comprehension or Actual Use studies would be required. Further discussion revealed that approvability would not require demonstration of a statistically significant difference between famotidine 20 mg and 10 mg, but rather demonstration of a dose response with a “clinically meaningful” difference. An endpoint of “complete prevention” (secondary endpoint) was considered a more clinically understandable measure of efficacy than “peak heartburn” (primary endpoint). FDA acknowledged that the 3 completed prevention studies (114, 117, 128) appeared to support the prevention indication, and that data from original NDA 20-325 treatment studies (017, 019) might support a relief indication for a 20 mg dose. At a June 20, 2002 teleconference meeting attended by Merck representatives and Drs. Raczkowski and Gallo-Torres of the GI Division, and Dr. Permutt of the Biometrics Division, concurrence was obtained on the statistical approaches that were proposed at the May 30th meeting. In a written communication to NDA 20-325 dated August 20, 2002, the Sponsor provided a summary of the sources of efficacy and safety data to be included in this SNDA.

D. Other Relevant Information

The active ingredient of the dosage forms of famotidine were licensed to Merck & Co., Inc., from Yamanouchi Pharmaceutical Company, Ltd. (Japan). Famotidine also may be referred to in this application by its code names MK-0208, L-000643341, and YM-11170. Famotidine products may be referred to by its trade names PEPCID™ and PEPCID™ AC and PEPCID™ COMPLETE (representing famotidine-antacid combination, PEPCID™/Antacid Combination, PEPCID™/Antacid Combination Chewable Tablet, and famotidine/antacid chewable tablet). Famotidine is a potent, competitive, and reversible inhibitor of histamine action at the H₂ receptor. PEPCID™ is currently available by prescription as 20 mg and 40 mg tablets, orally disintegrating tablets, oral suspension (40 mg/5 mL), and parenteral formulations for a variety of upper gastrointestinal disorders including (but not limited to) duodenal ulcer healing and post-healing maintenance, as well as for the relief of gastroesophageal reflux disease (GERD). The dosage regimens for the 40 mg and 20 mg prescription tablets are either once or twice daily. The proposed indications for an over-the-counter (OTC) 20 mg product are relief and/or prevention of heartburn symptoms using up to 2 tablets a day.

Table 1 lists 65 countries in which 10 mg famotidine is marketed. The sponsor believes that all 10 mg approvals listed in Table 1 are for a nonprescription drug. It is not known whether all registered products were actually launched. 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. The 10 mg products marketed in other countries are available to the consumer as a self-selection (general sales) product.

Table 1. Marketing 10 mg

Country	Tradename	Dosage form	Approval Date
Argentina	Efficid	Film-coated tablet	May-1997
Argentina	Unknown	Chewable	May-1997
Australia	Pepcid	Film-coated tablet	23-Jan-1996
Australia	Pepcid	Chewable	23-Jan-1996
Belgium	Pepcid AC	Film-coated tablet	April-1996
Canada	Pepcid AC	Film-coated tablet	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	Film-coated tablet	24-Jun-1994
Finland	Pepcid	Film-coated tablet	May-1996
Finland	Pepcid	Chewable	May-1996 (withdrawn May-2001)
Finland	PEPCID DUO [†]	Chewable	02-Sep-2000
France	Pepcid AC	Film-coated tablet	21-Mar-1996
France	Pepcid AC	Chewable	21-Mar-1996 (not marketed)
France	PEPCIDDUO [†]	Chewable	22-Feb-2000
French Guiana	Pepcid AC	Film-coated tablet	21-Mar-1996
French Guiana	Pepcid AC	Chewable	21-Mar-1996
French Polynesia	Pepcid AC	Film-coated tablet	21-Mar-1996
French Polynesia	Pepcid AC	Chewable	21-Mar-1996
Germany	Pepcid akut	Film-coated tablet	23-Dec-1997
Germany	Mylanta	Film-coated tablet	23-Dec-1997 (not marketed)
Germany	PEPCIDDUAL [†]	Chewable	28-Mar-2001
Guadeloupe	Pepcid AC	Film-coated tablet	21-Mar-1996
Guadeloupe	Pepcid AC	Chewable	21-Mar-1996
Hong Kong	Unknown	Film-coated tablet	Jul-1995
Iceland	Pepcid AC	Film-coated tablet	Oct-1995
Iceland	Pepcid AC	Chewable	Oct-1995
Ireland	Pepcid AC	Film-coated tablet	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	Film-coated tablet	Jul-1997
Malaysia	Pepcid AC	Film-coated tablet	24-Dec-1998
Martinique	Pepcid AC	Film-coated tablet	21-Mar-1996
Martinique	Pepcid AC	Chewable	21-Mar-1996
Mayotte	Pepcid AC	Film-coated tablet	21-Mar-1996
Mayotte	Pepcid AC	Chewable	21-Mar-1996
Mexico	Pepcid AC	Film-coated tablet	27-Jan-1995
Netherlands	Pepcidin AC	Film-coated tablet	16-May-1995

Netherlands	Pepcidin AC	Chewable	16-May-1995 (not marketed)
New Caledonia	Pepcid AC	Film-coated tablet	21-Mar-1996
New Caledonia	Pepcid AC	Chewable	21-Mar-1996
New Zealand	Pepcid AC	Film-coated tablet	08-Sep-1994
New Zealand	Pepcid AC	Chewable	17-Apr-1997
Norway	Pepcid AC	Film-coated tablet	Jan-1997
Norway	Pepcid AC	Chewable	Oct-1997 (withdrawn Mar-2000)
Norway	PEPCID DUO [†]	Chewable	11-Jan-2001
Reunion	Pepcid AC	Film-coated tablet	21-Mar-1996
Reunion	Pepcid AC	Chewable	21-Mar-1996
Singapore	Pepcid AC	Film-coated tablet	29-Mar-1996
Spain	PEPCID	Film-coated tablet	13-May-1998
Spain	PEPCID	Chewable	02-Aug-2001 (not marketed)
Spain	PEPDUAL [†]	Chewable	03-Aug-2001
Sweden	Pepcid AC	Film-coated tablet	Mar-1995
Sweden	Pepcid	Chewable	Mar-1995 (withdrawn Jun-2000)
Sweden	PEPCID DUO [†]	Chewable	23-Mar-2001
Switzerland	Pepcid AC	Film-coated tablet	13-Dec-1996
Switzerland	Pepcid AC	Chewable	13-Dec-1996
United Kingdom	Pepcid AC/Boots Excess Acid Control [§]	Film-coated tablet	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	Film-coated tablet	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.

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 summarizes marketing experience in 70 countries for the 20 mg famotidine product, and Table 3 summarizes marketing experience in 80 countries for the 40 mg product. To the best of the Sponsor's 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).

Table 2. 20 mg Marketing

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
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.

Table 3. Marketing 40 mg

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	20-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
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
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.

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

Table 4. Marketing Withdrawals

Country	Tradename	Dosage	Type	Approval Date	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 [§]

E. Important Issues with Pharmacologically Related Agents

The prescription labeling for cimetidine, ranitidine, nizatidine and famotidine (all of which are H₂ blockers available OTC) includes directions to reduce the dosing schedule in patients with renal insufficiency. For ranitidine, nizatidine and famotidine, the direction is to adjust the dosage for patients with creatinine clearance <50 mL/min. For cimetidine, the dose should be reduced in patients with 'severely impaired renal function', no specific criterion defined.

Severe liver toxicity has been reported in association with use of two H₂ blockers, ebrotidine and niperotidine, which structurally related to ranitidine and famotidine, but differ in the composition of the side chain. Ebrotidine was withdrawn from marketing in Spain for safety reasons [Micromedex].

References

Andrade RJ, Lucena MI, Martin-Vivaldi R et al: Acute liver injury associated with the use of ebrotidine, a new H₂- receptor antagonist. J Hepatol 1999; 31:641-646.

Jimenez-Saenz M, Arguelles-Arias F, Herreras-Gutierrez JM, Duran-Quintana JA: Acute cholestatic hepatitis in a child treated with famotidine. Am J Gastroenterol 2000;95(12):3665-6.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

See separate efficacy, statistical and chemistry reviews for this application. There were no new toxicology studies submitted with this application.

III. Human Pharmacokinetics and Pharmacodynamics

The famotidine 20 mg formulation used in Protocols 117, 118, 119, 128, and 137 is the proposed 20 mg nonprescription formulation. The formulation used in Protocol 114 is identical except for the color, which would not be expected to affect in vivo performance of the tablet. Protocols 017-01 and 019-00 were previously reviewed and approved (28-Apr-1995) under the original submission for NDA 20-325. The investigational formulations for those 2 studies would be expected, based on similarities in composition, manufacturing, and dissolution behavior, to perform similarly in vivo to the proposed 20 mg OTC formulation. All famotidine formulations used in the clinical studies referenced in this submission are therefore identical or nearly identical in terms of composition and manufacturing. Bioequivalence studies comparing these formulations were therefore not necessary.

The development of nonprescription famotidine 20 mg tablets was based on extensive experience with the prescription product. The unit formula (with the exception of the deletion of colorant) is identical to the currently approved prescription product. The composition includes the same excipients that are used in both the prescription product as well as the nonprescription 10 mg product. Proposed manufacturing sites for routine production batches of the nonprescription formulation are identical to those for the currently approved prescription product and the 10 mg nonprescription product.

The 20 mg strength nonprescription famotidine tablets would be marketed as a white, "D"-shaped tablet, plain on one side and debossed with "PAC 20" on the other.

A. Pharmacokinetics

Data relating to pharmacokinetics and bioavailability of famotidine were previously submitted in the original NDA 19-462. Complete information can be found in the Human Pharmacokinetics and Bioavailability Technical Section of the Tablets PEPCID™ (famotidine, MSD) NDA 19-462.

The pharmacokinetics section of the prescription famotidine label is reproduced below:

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

an oral dose and 65-70% of an intravenous dose are recovered in the urine as unchanged compound. The only metabolite identified in man is the S-oxide. There is a close relationship between creatinine clearance values and the elimination half-life of PEPCID. In patients with severe renal insufficiency, i.e., creatinine clearance less than 10 mL/min, the elimination half-life of PEPCID may exceed 20 hours and adjustment of dose or dosing intervals in moderate and severe renal insufficiency may be necessary (see PRECAUTIONS , DOSAGE AND ADMINISTRATION).

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

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

Dosage Adjustment for Patients with Moderate or Severe Renal Insufficiency

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

B. Pharmacodynamics

The following pharmacodynamics study was submitted as part of the current application. The objective of the current study was to compare the gastric antisecretory activity of 10 mg versus 20 mg of famotidine, given 10 minutes prior to a provocative evening meal.

Study P118: A Double-Blind, Three-Period, Crossover Study to Compare the Effect of Famotidine 20 mg, Famotidine 10 mg, and Placebo on Gastric and Esophageal pH Profiles in Patients Who Experience Heartburn

INVESTIGATOR(S)/STUDY CENTER(S): Michael S. Epstein, M.D.; Annapolis, MD, USA

PRIMARY THERAPY PERIOD: 12-Jun-1998 to 08-Aug-1998. All case report forms were received in Merck Research Laboratories by 19-Aug-1998. The study is complete.

CLINICAL PHASE: III DURATION OF TREATMENT: A single dose was given in each of 3 treatment periods to be separated by 5 to 7 days. The study duration from first-patient-in to last-patient-out was approximately 5 months.

OBJECTIVE(S): To compare the activity of 10 and 20 mg of famotidine, given 10 minutes prior to a provocative evening meal, on gastric pH as measured by area under the pH versus time curve during the 1.5- to 13.5-hours postdose interval (the 12-hour interval of time ending immediately prior to the 8:30 AM breakfast).

STUDY DESIGN: Double-blind, crossover, placebo-controlled, single-center study.

Table 5. P118 Patient accounting

	F20/F10/P	F10/P/F20	P/F20/F10	F20/P/F10	F10/F20/P	P/F10/F20	Total
Entered total	4	4	4	4	4	4	24
Male (age)	2 (39 to 48)	0	2 (21 to 44)	2 (37 to 48)	0	0	6 (21 to 48)
Female (age)	2 (18 to 49)	4 (30 to 49)	2 (49 to 49)	2 (39 to 48)	4 (35 to 49)	4 (26 to 45)	18 (18 to 49)
Completed	4	4	4	4	4	4	24
Discontinued	0	0	0	0	0	0	0

DIAGNOSIS/INCLUSION CRITERIA: Males and females between the ages of 18 and 50 years old with a history of food-induced heartburn of at least 2-months duration with at least 3 episodes per week. Patients with history of serious medical conditions or evidence of impaired renal function were excluded.

EVALUATION CRITERIA: Gastric: areas under the pH/time curves, % of pH readings >3. Esophageal: area under the pH/time curves, % time pH <4, number and duration of reflux episodes.

STATISTICAL PLANNING AND ANALYSIS: Area under the intragastric pH versus time curve measured 1.5 to 13.5 hours postdose was analyzed using an analysis of variance (ANOVA) model that included factors for treatment, period, treatment sequence, patient-within-treatment sequence, and carryover effect. A logarithmic transformation was used to satisfy the assumptions of the analysis. A sample size of 24 patients would provide 87% power to detect a geometric mean ratio (famotidine 20 mg/famotidine 10 mg) of 1.28 or greater assuming $\alpha=0.050$, two-tailed, and a mean square error of 0.079 on the log-transformed scale. Descriptive statistics and confidence intervals for all pairwise treatment comparisons are presented. All p-values were rounded to three decimal places, and statistical significance was declared if the rounded p-value was <0.050.

RESULTS: Efficacy

The highest mean AUC was seen with famotidine 20 mg (Table 6), indicating that the increase of intragastric pH was greatest with famotidine 20 mg, during the 12-hour interval ending immediately prior to the 8:30 AM breakfast. The mean gastric pH for famotidine 20 mg was higher by 0.5 pH units than for famotidine 10 mg ($p=0.007$). Therefore, post-meal acid exposure was lowest for the 20-mg treatment when compared to 10-mg and placebo.

Table 6. Mean Area under Intra-gastric pH/Time Curve 1.5 to 13.5 Hours Postdose (N=24)

Treatment	Geometric Mean	Logarithm of Geometric Mean	
		Mean	Standard Error
Famotidine 20 mg	2.64	0.97	0.053
Famotidine 10 mg	2.13	0.76	0.053
Placebo	1.35	0.30	0.053

Treatment Comparison	Geometric Mean Ratio (95% CI)	Increase	p-Value
Famotidine 20 mg/famotidine 10 mg	1.24 (1.06, 1.44)	24%	0.007*
Famotidine 20 mg/placebo	1.96 (1.68, 2.28)	96%	<0.001*
Famotidine 10 mg/placebo	1.58 (1.36, 1.84)	58%	<0.001*

Note: Famotidine 20 mg versus famotidine 10 mg was the primary treatment comparison.
* p<0.050.

According to Table 7, the highest percentage of pH values >3.0 was seen with famotidine 20 mg, indicating that the increase of intra-gastric pH was greatest with famotidine 20 mg.

Table 7. Percentage of Intra-gastric pH Values >3.0: 1.5 to 13.5 Hours Postdose (N=24)

Treatment	Adjusted Mean†	Transformed Mean‡	
		Mean	Standard Error
Famotidine 20 mg	32.65%	0.61	0.032
Famotidine 10 mg	21.37%	0.48	0.032
Placebo	5.83%	0.24	0.032

Treatment Comparison	p-Value
Famotidine 20 mg/famotidine 10 mg	0.007*
Famotidine 20 mg/placebo	<0.001*
Famotidine 10 mg/placebo	<0.001*

† Mean resulting from analysis transformed back to a percentage.
‡ Mean on transformed scale (adjusted for factors in the model).
* p<0.050.

During the nocturnal period after the provocative meal (4 to 12 hours postdose, see Table 8), the highest mean AUC was seen with famotidine 20 mg, indicating that the increase of intra-gastric pH was greatest with famotidine 20 mg.

Table 8. Mean Area Under the Intra-gastric pH/Time Curve: 4 to 12 Hours Postdose (N=24)

Treatment	Geometric Mean	Logarithm of Geometric Mean	
		Mean	Standard Error
Famotidine 20 mg	2.50	0.92	0.061
Famotidine 10 mg	2.01	0.70	0.061
Placebo	1.25	0.22	0.061

Treatment Comparison	Geometric Mean Ratio (95% CI)	Increase	p-Value
Famotidine 20 mg/Famotidine 10 mg	1.24 (1.04, 1.47)	24%	0.016*
Famotidine 20 mg/Placebo	2.00 (1.69, 2.38)	100%	<0.001*
Famotidine 10 mg/Placebo	1.62 (1.36, 1.92)	62%	<0.001*

* p<0.050.

Table 9 displays the mean area under the intraesophageal pH/time curve during the 40- to 220-minute postdose period (3-hour interval of time starting at the completion of the provocative meal). Both active treatments had a higher mean AUC than placebo; however, the treatment comparisons were not significant ($p \geq 0.088$). The difference between famotidine 20 mg and famotidine 10 mg was not significant ($p=0.881$).

Table 9. Mean Area Under the Intra-Esophageal pH/Time Curve: 40 to 220 Minutes Postdose

Treatment	Geometric Mean	Logarithm of Geometric Mean	
		Least Squares Mean	Standard Error
Famotidine 20 mg	5.70	1.74	0.022
Famotidine 10 mg	5.73	1.75	0.022
Placebo	5.43	1.69	0.022

Treatment Comparison	Geometric Mean Ratio (95% CI)	Increase	p-Value
Famotidine 20 mg/famotidine 10 mg	1.00 (0.94, 1.06)	0%	0.881
Famotidine 20 mg/placebo	1.05 (0.99, 1.12)	5%	0.118
Famotidine 10 mg/placebo	1.05 (0.99, 1.12)	5%	0.088

None of these comparisons were statistically significant.

Reflux episodes were defined, for the purposes of this study, defined as a fall of esophageal pH from 5.0 or above to below 4.0. The numbers of reflux episodes, for the interval 40 to 220 minutes postdose, are not significantly different between famotidine 20 mg and famotidine 10 mg. Only famotidine 10 mg was found to be significantly different from placebo ($p=0.047$).

Safety: There were no clinical adverse experiences reported during this study.

P118 CONCLUSIONS: During the 1.5- to 13.5-hour postdose period, famotidine 20 mg produces a higher gastric pH (lower acidity) than famotidine 10 mg and placebo as measured by mean area under the intragastric pH/time curve and the percentage of time when intragastric pH is >3.0. Also, during the 4- to 12-hour postdose nocturnal period with patients in bed, famotidine 20 mg produces a higher gastric pH than famotidine 10 mg and placebo as measured by the mean area under the intragastric pH/time curve. However, all comparisons of effects on intra-esophageal pH, from 40 to 220 minutes after dosing, did not reach statistical significance, except for the comparison of famotidine 10 mg with placebo in number of reflux episodes. In particular, famotidine 20 mg was not shown to have significantly more efficacy than famotidine 10 mg for number of reflux episodes and intra-esophageal pH endpoints. All treatments are well tolerated.

IV. Description of Clinical Data and Sources

A. Overall Data

The following data were used in this review. Aside from P118, only safety results from the prevention and supportive studies listed in Table 10 are reviewed here. Also, reference is made to the review of two famotidine heartburn relief studies (P017, P019) submitted for NDA 20-325, written by Dr. Robie-Suh on 1/12/94. Worldwide post-marketing surveillance and literature were reviewed.

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B. Tables Listing the Clinical Trials

The following table lists the studies that were submitted in this application.

Table 10. Clinical Studies for NDA 20-325/Supplement-015

Study P114	Multicenter Study: A Randomized, Single-Dose Study Comparing Famotidine 20 mg, Famotidine 10 mg, and Placebo in Preventing Heartburn Symptoms When Administered 10 Minutes Prior to a Provocative Meal
Study P117	Multicenter Study: A Randomized, Single-Dose, Double-Blind, Parallel Study Comparing Famotidine 20 mg, Famotidine 10 mg, and Placebo in Preventing Heartburn Symptoms When Administered 10 Minutes Prior to a Provocative Meal
Study P118	A Double-Blind, Three-Period, Crossover Study to Compare the Effect of Famotidine 20 mg, Famotidine 10 mg, and Placebo on Gastric and Esophageal pH Profiles in Patients Who Experience Heartburn
Study P119	Multicenter Study: An Open-Label Study to Evaluate Patterns of Use of Famotidine 20 mg Tablets in Patients with Episodic Heartburn
Study P128	Multicenter Study: An In-Clinic, Randomized, Single-Dose, Double-Blind, Parallel Study Comparing Famotidine 20 mg, Famotidine 10 mg, and Placebo in Preventing Heartburn Symptoms When Administered Prior to a Provocative Meal
Study P137	A Randomized, Double-Blind, Multidose, Pilot Study Comparing the Efficacy of Famotidine 20 mg and Placebo in Preventing Heartburn and Acid Reflux When Administered Immediately Prior to a Provocative Meal
Study P017	Multicenter Study: A Double-Blind, Dose Ranging Study to Evaluate the Effects of Doses as Needed up to Twice Daily of Famotidine 5 mg, 10 mg, 20 mg, or Antacid, as Compared to Placebo in the Treatment of Intermittent Heartburn
Study P 019	Multicenter Study: A Double-Blind, Dose Ranging Study to Evaluate the Effects of Famotidine 10 mg, 20 mg, or Antacid, as Compared to Placebo as Needed up to Twice Daily in the Treatment of Intermittent Heartburn

C. Postmarketing Experience

The sponsor provided access to postmarketing data for this review.

D. Literature Review

The sponsor provided a summary of literature for this review.

V. Clinical Review Methods

A. Description of How Review was Conducted

All prevention and supportive trials were reviewed separately for safety by the present reviewer. P118 is also reviewed in its entirety in the PK/PD section. The original reviews of studies P017 and P019 for the Pepcid AC heartburn relief

claim were referenced. Some literature reports were reviewed. Post-marketing surveillance reports were evaluated and analyzed.

B. Overview of Materials Consulted in Review

No IND(s) were evaluated for this application. See Section A.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

No DSI audits were requested.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Yes.

E. Evaluation of Financial Disclosure

There were no financial disclosures that would cast doubt on the findings.

VI. Integrated Review of Efficacy

Refer to review by Dr. Lopez, HFD-180.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The analysis of the submitted clinical trial safety data shows that famotidine is generally well tolerated in doses up to 20 mg twice daily when used for relief or prevention of episodic heartburn. The safety profile of famotidine in the clinical trials was similar for famotidine 20 mg and 10 mg, and there are no clinically meaningful differences in the safety profile with regard to gender, age, or race. Appendix B lists the most common adverse events (AEs) mentioned in post-marketing reports from health care professionals. Reviews of postmarketing reports and the clinical literature revealed the rare occurrence of the following unlisted events, for which the relationship to therapy may be unclear: aplastic anemia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, QT prolongation, rhabdomyolysis, hepatic necrosis, hepatic failure, hepatitis, mixed hepatocellular jaundice, pancreatitis, and carcinoid tumor.

The postmarketing reports revealed an increased number of serious adverse events involving famotidine daily doses of 40 mg compared to daily doses of 20 mg or 10 mg.

B. Description of Patient Exposure

Table 11. Summary of Clinical Trials for Prevention Claim

Protocol Number	Reference Number	Short Study Description	Study Drug	Duration of Treatment	Number Evaluable for Safety
Primary Studies for Evaluation of Safety (“Prevention Studies”)					
114	[P114]	Double-blind, randomized, single-dose, parallel study to assess efficacy in prevention of heartburn	Famotidine 20 mg Famotidine 10 mg Placebo	1 day	794
117 [†]	[P117]	Double-blind, randomized, single-dose, parallel study to assess efficacy in prevention of heartburn	Famotidine 20 mg Famotidine 10 mg Placebo	1 day	1229
128	[P128]	Double-blind, randomized, single-dose, parallel study to assess efficacy in prevention of heartburn	Famotidine 20 mg Famotidine 10 mg Placebo	1 day	1334
137	[P137]	Double-blind, randomized, multidose, pilot study to assess efficacy in prevention of heartburn and acid reflux	Famotidine 20 mg Placebo	2 weeks (4 doses)	287
Supportive Studies for Evaluation of Safety					
118	[P118]	Double-blind, crossover, single-dose, pharmacodynamic study measuring gastric and esophageal pH in patients who experience heartburn	Famotidine 20 mg Famotidine 10 mg Placebo	1 day (each period)	24
119	[P119]	Open-label, uncontrolled, multiple-dose, pattern of use study	Famotidine 20 mg	3 weeks	523
[†] A subset of patients (n=128) from Protocol 117 participated in a multicenter endoscopy study (Protocol 120). No drug was administered in Protocol 120; therefore, safety results are not included in the integrated tables. See the Protocol 120 Clinical Study Report Synopsis [26] for study details. Note: Data are included in Item 11 for patients who participated in the screening phase for the Prevention Studies, but were never randomized. Treatment group name is listed as “Baseline” for these nonrandomized patients.					

The sponsor provided a summary of six clinical trials reported in support of a prevention indication (Table 11). The total number of patients evaluable for safety in these trials was 4191, of whom 3381 subjects received only a single dose of either famotidine 20 mg, famotidine 10 mg, or placebo. Another 287 subjects in P137 received a total of 4 doses each over 2 weeks of either famotidine 20 mg or placebo. The remaining 523 subjects (in P119) were given 50 tablets of famotidine 20 mg to self-medicate over 3 weeks.

In the six prevention and supportive trials, the total number of patients exposed to at least one dose of famotidine 20 mg was 1972. Of these, 1306 (66%) took single doses in controlled studies, and another 143 (7.3%) took four doses in the controlled study P137. In the use study P119, a total of 523 subjects took from 1 to 50 tablets over a three-week study period, but the median total number of tablets taken was 16 tablets (see Table 12 and Figure 1 on page 33).

Table 12.**Number of Subjects/Patients by Maximum Number of Doses Taken and Treatment Group**

	Famotidine 20 mg	Famotidine 10 mg	Placebo
Subjects			
Single-dose study [†]	24	24	24
Patients			
Single-dose studies [‡]	1282	1299	776
Four-dose study [§]	143	0	144
Actual Use study (≤50 doses)	523	0	0
Total number of unique individuals per treatment group	1972	1323	944
[†] Protocol 118. This was a crossover study in 24 subjects. The 24 subjects are presented separately for each treatment they received. Since these 24 subjects are each counted 3 times, the total number of subjects/patients across treatment groups does not equal the total number of subjects/patients studied. [‡] Protocols 114, 117, and 128. [§] Protocol 137. Protocol 119.			

C. Methods and Specific Findings of Safety Review

This section includes:

- safety reviews for studies P114, P117, P128, P137, and P119.
- published literature
- data on worldwide postmarketing surveillance.

STUDY P114: A Randomized, Single-Dose Study Comparing Famotidine 20 mg, Famotidine 10 mg, and Placebo in Preventing Heartburn Symptoms When Administered 10 Minutes Prior to a Provocative Meal

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter, U.S.A.

PRIMARY THERAPY PERIOD: 14-Jan-1998 to 17-Mar-1998. Study is complete. All case report forms received at MRL by 17-May-1998

DURATION OF TREATMENT: The study included a 3-hour screening meal session and 3-hour treatment meal session followed by at-home evaluation period until 8 AM the following morning. The study lasted 8 weeks.

OBJECTIVE: To assess the ability of famotidine 20 mg and famotidine 10 mg to prevent heartburn in patients treated 10 minutes prior to an evening provocative meal.

STUDY DESIGN: Double-blind, randomized, double-dummy, single-dose, placebo-controlled, multicenter trial conducted with 3 parallel groups (Table 13).

Table 13. P114 patient accounting

	Famotidine 20 mg	Famotidine 10 mg	Placebo	Total
ENTERED: Total Randomized	261	271	262	794
Male (age range)	87 (19 to 67)	87 (20 to 70)	84 (21 to 77)	258 (19 to 77)
Female (age range)	174 (19 to 81)	184 (19 to 72)	178 (18 to 74)	536 (18 to 81)
COMPLETED:	261	270	262	793
DISCONTINUED: Total	0	1	0	1
Patient Uncooperative	0	1	0	1

DOSAGE/FORMULATION: Each patient took a single dose of 1 Famotidine 10 mg Film-Coated Tablet Matching Placebo at the screening meal, and a single dose of 2 tablets (one active, one placebo or two placebo) at the treatment meal.

DIAGNOSIS/INCLUSION CRITERIA: Male or female patients at least 18 years of age with a history of food-induced heartburn of at least 2 months' duration with at least 3 episodes per week of moderate to severe intensity, and who use antacids or OTC acid reducers. Those with a history of serious medical conditions or evidence of impaired renal function were excluded.

SAFETY: Adverse experiences were reported during the screening and treatment meal sessions through 8 AM the following morning.

Safety Results: (All-Patients-Treated)

Table 14. P114: Clinical adverse experiences (AEs)

	Famotidine 20 mg		Famotidine 10 mg		Placebo	
	(n=261)		(n=271)		(n=262)	
Number (%) of patients:	n	(%)	n	(%)	n	(%)
With one or more AEs	9	(3.4)	10	(3.7)	10	(3.8)
With no AEs	252	(96.6)	261	(96.3)	252	(96.2)
With drug-related AEs	1	(0.4)	2	(0.7)	2	(0.8)
With serious AEs	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to an AE	0	(0.0)	0	(0.0)	0	(0.0)

As demonstrated in Table 14, both famotidine 20 mg and famotidine 10 mg were well tolerated. There were no serious AEs, and the numbers of reported AEs were similar for the two famotidine formulations and placebo. The most commonly reported AE for famotidine 20 mg was headache (5 reports, see Appendix A).

STUDY P117: A Randomized, Single-Dose, Double-Blind, Parallel Study Comparing Famotidine 20 mg, Famotidine 10 mg, and Placebo in Preventing Heartburn Symptoms When Administered 10 Minutes Prior to a Provocative Meal

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter—Thirteen investigators. All 13 sites were located in the United States.

PRIMARY THERAPY PERIOD: Jul-1998 to Sep-1998 The study is complete. All case report forms were received by Merck Research Laboratories by 21-Dec-1998.

DURATION OF TREATMENT: Qualified patients received a dose of study medication 10 minutes prior to a provocative meal. Heartburn severity was evaluated for 3 hours following the meal.

OBJECTIVE(S): To assess the ability of famotidine 20 mg and famotidine 10 mg to prevent heartburn in patients treated 10 minutes prior to an evening provocative meal.

STUDY DESIGN: Double-blind, randomized, double-dummy, single-dose, placebo-controlled, multicenter trial conducted with 3 parallel groups (see Table 15).

Table 15. P117 patient accounting

	Famotidine 20 mg	Famotidine 10 mg	Placebo	Total
ENTERED: Total Randomized	489	491	249	1229
Male (age range)	190 (18 to 76)	199 (19 to 73)	105 (20 to 78)	494 (18 to 78)
Female (age range)	299 (18 to 80)	292 (19 to 85)	144 (18 to 78)	735 (18 to 85)
COMPLETED:	488	489	248	1225
DISCONTINUED: Total	1	2	1	4
CLINICAL AE	0	0	1	1
LOST TO FOLLOW UP	0	1	0	1
PROTOCOL DEVIATION	1	1	0	2

DOSAGE/FORMULATION: Each patient took a single dose consisting of 2 film-coated tablets (1 active and 1 placebo or 2 placebos).

DIAGNOSIS/INCLUSION CRITERIA: Male and female patients at least 18 years of age with a history of food-induced heartburn of at least 2 months' duration with at least 3 episodes per week. Patients must have experienced heartburn which was frequently severe, (30% of their episodes; heartburn severity was determined by self-evaluation). Patients must have been able to identify specific foods and beverages that produced their symptoms. Those with evidence of impaired renal function were excluded.

SAFETY: Adverse experiences were monitored throughout this study; nonserious adverse experiences were recorded during the baseline run-in and treatment session through 8 AM the following morning.

Safety Results: (All-Patients-Treated)

Table 16. P117 Clinical adverse experiences (AEs)

	Famotidine 20 mg		Famotidine 10 mg		Placebo	
	(n=489)		(n=491)		(n=249)	
Number (%) of patients:	n	(%)	n	(%)	N	(%)
with one or more AEs	12	(2.5)	16	(3.3)	11	(4.4)
with no AEs	477	(97.5)	475	(96.7)	238	(95.6)
with drug-related AEs	3	(0.6)	6	(1.2)	5	(2.0)
with serious AEs	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to an AE	0	(0.0)	0	(0.0)	0	(0.0)

As demonstrated in Table 16, both famotidine 20 mg and famotidine 10 mg were well tolerated. There were no serious AEs, and the numbers of reported AEs were similar for the two famotidine formulations and placebo. The most commonly reported AE for

famotidine 20 mg was headache (7 reports, see Appendix A). One 31 year old subject had an adverse experience coded as “pain, chest” which was assessed as not serious.

STUDY P128: An In-Clinic, Randomized, Single-Dose, Double-Blind, Parallel Study Comparing Famotidine 20 mg, Famotidine 10 mg, and Placebo in Preventing Heartburn Symptoms When Administered Prior to a Provocative Meal

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter—Fifteen investigators. All 15 sites were located in the United States.

PRIMARY THERAPY PERIOD: Apr-1999 to May-1999. The study is complete. All case report forms were received by Merck Research Laboratories by 9-Feb-2000.

DURATION OF TREATMENT: Qualified patients received a dose of study medication 10 minutes prior to a provocative meal. Heartburn severity was evaluated for 3 hours following the meal.

OBJECTIVE(S): To assess the ability of famotidine 20 mg and famotidine 10 mg to prevent heartburn in patients treated 10 minutes prior to an evening provocative meal.

STUDY DESIGN: Double-blind, randomized, double-dummy, single-dose, placebo-controlled, multicenter trial conducted with 3 parallel groups (see Table 17).

Table 17. P128 patient accounting

	Famotidine 20 mg	Famotidine 10 mg	Placebo	Total
ENTERED: Total Randomized	532	537	265	1334
Male (age range)	187 (18 to 77)	189 (19 to 81)	101 (19 to 77)	477 (18 to 81)
Female (age range)	345 (18 to 77)	348 (19 to 82)	164 (19 to 81)	857 (18 to 82)
COMPLETED:	529	536	265	1330
DISCONTINUED: Total	3	1	0	4
Clinical Adverse Experience	1	1	0	2
Unbearably Severe UGI Symptoms	2	0	0	2

DOSAGE/FORMULATION: Each patient took a single dose consisting of 2 film-coated tablets (1 active and 1 placebo or 2 placebos).

DIAGNOSIS/INCLUSION CRITERIA: Male and female patients at least 18 years of age with a history of food-induced heartburn of at least 2 months’ duration with at least 3 episodes per week. Patients must have experienced heartburn which was frequently severe, (≥30% of their episodes; heartburn severity was determined by self-evaluation). Patients must have been able to identify specific foods and beverages that produced their symptoms. Those with a history of serious medical conditions or evidence of impaired renal function were excluded.

SAFETY: Adverse experiences were monitored throughout this study; nonserious adverse experiences were recorded during the baseline run-in and treatment session through 8 AM the following morning.

Safety Results: (All-Patients-Treated)

Table 18. P128 Clinical adverse experiences (AEs)

	Famotidine 20 mg	Famotidine 10 mg	Placebo
	(n=532)	(n=537)	(n=265)
Number (%) of patients:	n(%)	n(%)	n(%)
with one or more AEs	4 (0.8)	5 (0.9)	2 (0.8)
with no AEs	528 (99.2)	532 (99.1)	263 (99.2)
with drug-related AEs†	1 (0.2)	1 (0.2)	0 (0.0)
with serious AEs	0 (0.0)	0 (0.0)	0 (0.0)
with serious drug-related AEs	0 (0.0)	0 (0.0)	0 (0.0)
discontinued drug due to an AE	2 (0.4)	0 (0.0)	0 (0.0)

† Adverse experiences considered by the investigator to be possibly related to study drug (there were no adverse experiences in this study that were considered to be probably or definitely related to study drug).

As Table 18 demonstrates, both famotidine 20 mg and famotidine 10 mg were well tolerated. There were no serious AEs, and the numbers of reported AEs were similar for the two famotidine formulations and placebo. The most commonly reported AEs for famotidine 20 mg were headache (3 reports) and vomiting (2 reports, see Appendix A). The 2 subjects on famotidine 20 mg listed in Table 17 as having discontinued due to "unbearably severe UGI pain" were included by the reviewer as having AEs in Table 18.

Study P137 A Randomized, Double-Blind, Multidose, Pilot Study Comparing the Efficacy of Famotidine 20 mg and Placebo in Preventing Heartburn and Acid Reflux When Administered Immediately Prior to a Provocative Meal

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter; 7 investigators; USA

PRIMARY THERAPY PERIOD: Study Dates: 06-Sep-2000 to 20-Mar-2001. Therapy dates: 21-Sep-2000 to 14-Mar-2001. In-house case report form cutoff was 29-Mar-2001.

DURATION OF TREATMENT: Patients underwent a 2-week baseline run-in period to see if they qualified for the double-blind treatment period. Once qualified, patients had 2 weeks to use 4 doses of double-blind medication.

OBJECTIVE(S): To assess the ability of famotidine 20 mg to prevent heartburn and symptomatic acid reflux in patients dosed immediately prior to a self-selected provocative meal.

STUDY DESIGN: Randomized, double-blind, multicenter, multidose, placebo-controlled, pilot study (see Table 19).

DOSAGE/FORMULATION NOS.: Each patient took 4 single doses consisting of either 1 active or 1 placebo tablet of study medication over a 2-week period.

DIAGNOSIS/INCLUSION CRITERIA: Male and female patients at least 18 years of age with a history of food-induced heartburn of at least 2 months' duration. Patients were able to identify specific foods and beverages that produced symptoms of heartburn. Those with a history of serious medical conditions or evidence of impaired renal function were excluded.

Table 19. P137 Patient accounting

	Famotidine 20 mg	Placebo	Total
ENTERED: Total	143	144	287
Male (age range—years)	68 (18 to 85)	74 (21 to 76)	142 (18 to 85)
Female (age range—years)	75 (18 to 76)	70 (18 to 75)	145 (18 to 76)
COMPLETED:	141	140	281
DISCONTINUED: Total	2	4	6
Lost to follow-up	2	2	4
Patient withdrew from study	0	1	1
Diary not returned	0	1	1

Three hundred eighty-nine patients entered baseline run-in period; 287 qualified for randomization.

SAFETY: Adverse experiences

Safety Results: (All-Patients-Treated)

Table 20. P137 Adverse Event Summary

	Famotidine 20 mg	Placebo
	(N=143)	(N=144)
Number (%) of patients:	n (%)	n (%)
with one or more AEs	9 (6.3)	13 (9.0)
with no AEs	134 (93.7)	131 (91.0)
with drug-related AEs [†]	2 (1.4)	5 (3.5)
with serious AEs	0 (0.0)	0 (0.0)
with serious drug-related AEs	0 (0.0)	0 (0.0)
discontinued drug due to an AE	0 (0.0)	0 (0.0)

[†] Adverse experiences considered by the investigator to be possibly or probably related to study drug (there were no adverse experiences in this study that were considered to be definitely related to study drug).

As Table 20 demonstrates, famotidine 20 mg was well tolerated. There were no serious AEs, and the numbers of reported AEs were similar for the famotidine 20 mg formulation and placebo. The most commonly reported AEs for famotidine 20 mg were headache (2 reports) and upper respiratory infection (2 reports, unrelated to study drug). A full AE listing is in the Appendix.

STUDY P119: An Open-Label Study to Evaluate Patterns of Use of Famotidine 20 mg Tablets in Patients with Episodic Heartburn

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter with nine investigators all in the United States

PRIMARY THERAPY PERIOD: Aug-1998 to Sep-1998. The study is complete. All case report forms were received by Merck Research Laboratories by 09-Oct-1998.

DURATION OF TREATMENT: The patient used the product over a 3-week period.

OBJECTIVE(S): To evaluate the patterns of use of famotidine 20-mg tablets among consumers who indicate a positive or neutral purchase interest in the product based on the product concept.

STUDY DESIGN: Open-label, multicenter, 3-week use study in patients who use antacids or H₂-receptor antagonists (OTC or prescription) for heartburn and who expressed a positive or neutral purchase interest in the product. Patients were provided

with famotidine 20 mg to administer at home. The labeled dose directions were for 2 tablets a day. (see Table 21 for patient accounting)

Table 21. P119 patient accounting

	Famotidine 20 mg
ENTERED: Total	523
Male (age range)	173 (18 to 83)
Female (age range)	350 (18 to 86)
COMPLETED:	510
DISCONTINUED: Total	13
Lost to follow-up	2
Completed/diary not returned	1
Patient withdrew from study	2
Study material lost	1
Family situation	1
Clinical adverse experience	6

DOSAGE/FORMULATION: Each patient received 50 tablets to be used over a 3-week period.

DIAGNOSIS/INCLUSION CRITERIA: Males or females, aged 18 years or older, who used antacids or H₂-receptor antagonists at least one time per week to treat or prevent their heartburn. Those with evidence of impaired renal function were excluded.

EVALUATION CRITERIA: Product use information was collected on diary cards (date and time of each dose and number of tablets taken). Safety and tolerability were assessed by monitoring for adverse experiences by the investigators or medically trained designees, at an office visit after the three week use period. The diary card instructed to patients to call the investigator if there were "any side effects or unusual symptoms" during the study.

STATISTICAL PLANNING AND ANALYSIS: Analysis of patterns of use was achieved through "noncompliance" and "summary of use" analyses utilizing counts tables of patient numbers in various categories. Analysis of safety data was achieved by tabulating the incidence of patient-reported clinical adverse experiences. Analyses included only patients who took at least 1 dose of medication. Sample size: n=400 patients was sufficient to estimate 95% confidence intervals with a width less than or equal to 9.8 percentage points for the true percentages of patients who: (1) took more than 2 tablets of study medication on at least 1 day during the study period, and (2) took more than 1 tablet as a single dose at least once during the study period (i.e., noncompliance parameters).

Results: Patterns of Use (All-Patients-Treated)

Study results showed that 84.9% of subjects complied with label instructions (see Table 22).

Table 22. P119 Use Patterns

	Famotidine 20 mg (N=515)	
	Number	(%)
Compliant with label instructions	437	(84.9)
Noncompliant with label instructions	78	(15.1)
Took >2 tablets/day at least once	16	(3.1)
Took >1 tablet/dose at least once	37	(7.2)
Noncompliant for both reasons	25	(4.9)

Number (%) of all doses when >1 tablet/dose was taken: 292/9610 (3.0%)

Number (%) of all days when >2 tablets/day were taken: 102/7250 (1.4%)

Although Table 22 states that 16 patients took more than 2 tablets on at least 1 day during the study period, the study report also gives the inconsistent information (on p.32 of the study report) that forty-one (8.0%) of the 515 patients eligible for the noncompliance analysis took more than 2 tablets on at least 1 day during the study period. Ten patients took at least twice the recommended dose on at least one day; of these, one took 5 tablets and another took 6 tablets. (see Table 23)

Table 23. Distribution of Patients by Maximum Dose Taken

Maximum Total Daily Dose	Number and Cumulative Percentages of Patients					
	Male		Female		Overall	
	n	Cum %	n	Cum %	n	Cum %
1	50	29.8	112	32.3	162	31.5
2	104	91.7	208	92.2	312	92.0
3	8	96.4	23	98.8	31	98.1
4	4	98.8	4	100.0	8	99.6
5	1	99.4	0	100.0	1	99.8
6	1	100.0	0	100.0	1	100.0
Total Patients	168		347		515	

Safety Results (Safety Population)**Table 24. P119 Safety Summary**

	Famotidine 20 mg (N=523)
Number (%) of Patients:	n(%)
With one or more AEs	46 (8.8)
With no AEs	477 (91.2)
With drug-related AEs	31 (5.9)
With serious AEs	0 (0.0)
Discontinued due to an AE	6 (1.1)
Discontinued due to drug-related AE	5 (1.0)

Table 24 demonstrates that famotidine 20 mg was well tolerated. There were no serious AEs, and 6 subjects (1.1%) discontinued (see Table 24) due to an AE (see Table 25).

Digestive system AEs were the most common (5%), followed by nervous system/psychiatric (2%); see Appendix A. One 27 year old subject had an adverse experience coded as “pain, chest” which was evaluated by the investigator to be not serious and possibly related to drug.

Table 25. Study P119 Discontinuations

AN	Study Number	Gender/Race/Age	Total Daily Dosage (Tablets)	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Relative Day of Discontinuance	Intensity	Drug Relationship	Serious	Outcome
0039	119001	Female/Caucasian/51	1 FAM 20 mg	2	Asthenia/fatigue	18 days	23	Mild	Possibly	No	Recovered
0046	119001	Female/Black/67	1 FAM 20 mg	2	Diarrhea	43 days	44	Mild	Prob. Not	No	Recovered
0203	119005	Female/Caucasian/71	1 FAM 20 mg	8	Dizziness	8 days	31	Mild	Possibly	No	Recovered
			1 FAM 20 mg	8	Tinnitus	8 days		Mild	Possibly	No	Recovered
0469	119010	Female/Caucasian/81	1 FAM 20 mg	1	Asthenia/fatigue	11 days	22	Mild	Possibly	No	Recovered
			1 FAM 20 mg	1	Somnolence	11 days		Mild	Possibly	No	Recovered
0480	119010	Female/Hispanic/42	1 FAM 20 mg	1	Headache	8 days	23	Mild	Possibly	No	Recovered
0485	119010	Female/Hispanic/51	1 FAM 20 mg	10	Pain, abdominal	7 hours	26	Moderate	Possibly	No	Recovered
			1 FAM 20 mg	10	Constipation	13 hours		Moderate	Possibly	No	Recovered

FAM = Famotidinc.

The average age of the safety population was 50.3 years (the median, 50 years).

The use study P119 also determined the distribution of patients by total dose taken (Figure 1). The maximum number of tablets taken in the study was 50 (all the tablets that were given to any subject), which was the total dose for 2 males and 2 females. The median number of tablets taken was 16. Overall, the total number of tablets taken by the highest number of patients was 9 tablets.

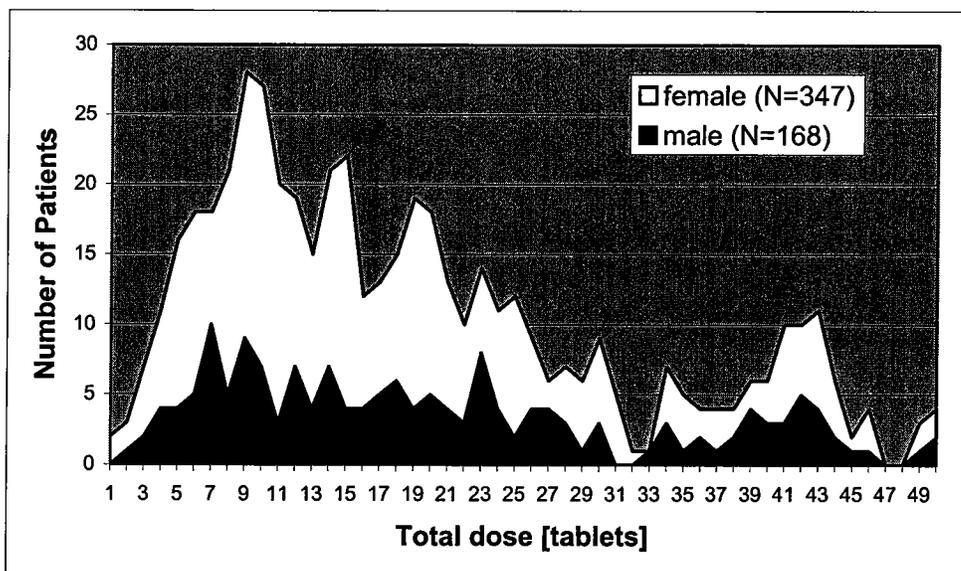


Figure 1. P119 Distribution of Patients by Total Dose

The following was a special non-drug safety study where endoscopic evaluation of the distal esophagus was performed in a subset of patients from Protocol 117.

STUDY P120: A Multicenter Study Assessing the Endoscopic Profile of Patients Who Are Self-Identified Severe Heartburn Sufferers

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter-five investigators in the United States

DURATION OF TREATMENT: The endoscopies were performed over a 5 month period period.

OBJECTIVE(S): To estimate the degree and distribution of esophagitis severity of severe heartburn sufferers over a 5-category Hetzel-Dent scale. A severe heartburn sufferer is defined as a patient with $\geq 30\%$ of their episodes rated severe by self-evaluation.

Esophagitis severity was measured on the 5-category Hetzel-Dent scale (Grade 0 to 4), with further exploratory classification (Grades 2A and 2B) for Grade 2 esophageal ulceration. Among the self-identified severe heartburn sufferers enrolled in this study, 32% were classified as having erosive esophagitis (Grades 2, 3, or 4), with 1.6% classified as having severe erosive esophagitis (Grade 4). In this study, one out of 128 patients was diagnosed with malignant esophageal neoplasm.

HEARTBURN RELIEF TRIALS

Two additional clinical studies (Protocols 017 and 019) are included in this application to support a relief of heartburn indication for nonprescription famotidine 20 mg. These studies were submitted in the original NDA for PEPCID™ AC 10 mg (NDA 20-325, approved 28-Apr- 1995) and are included in the present submission. These studies provide the primary safety data for the treatment indication.

Protocols 017 and 019 were randomized, double-blind, multicenter, parallel group trials. Patients self-treated as needed to treat their heartburn symptoms, up to twice daily. Double-blind study drug treatment was given for 4 weeks and was preceded by a 1-week run-in period which served to eliminate antacid non-responders. Both studies included the following treatment groups: placebo, antacid, famotidine 10 mg, and famotidine 20 mg that could use the medications up to twice daily.

Dr. Robie-Suh's review of these 2 studies, dated January 12, 1994, is referenced for safety. These studies are also being reviewed by HFD-180 for efficacy regarding the heartburn relief claim for the 20 mg tablet . A summary of Dr. Robie-Suh's safety review follows.

Table 26. Summary of Heartburn Relief Trials

Table of All Nonprescription Famotidine 20-mg Clinical Studies for Treatment Claim

Protocol Number	Reference Number	Short Study Title	Number Evaluable for Safety
017	[1]	Double-blind, placebo-controlled, dose ranging study to evaluate the efficacy of famotidine in the treatment of intermittent heartburn	565 [†]
019	[3]	Double-blind, placebo-controlled, dose ranging study to evaluate the efficacy of famotidine in the treatment of intermittent heartburn	509

[†] Of the 565 patients in Protocol 017, 113 patients were in the famotidine 5-mg treatment group. Data from this treatment group are not presented in the integrated tables, but are available in the individual Clinical Study Report [1].

Study 017 Double-blind, placebo-controlled, dose ranging study to evaluate the efficacy of famotidine in the treatment of intermittent heartburn

Safety: Adverse Event Summary

In this trial there were a total of 565 patients with 115 patients in the 20 mg arm and a similar number in the placebo, antacid, famotidine 10 mg, and famotidine 20 mg arms. Protocol 017 also included a famotidine 5-mg treatment group. All treatment groups could use their medications up to twice daily. There were no significant differences among the treatment groups in the numbers of patients experiencing adverse events. The percentage of patients having at least one event in the Digestive System was significantly greater for the famotidine 5mg group than for the famotidine 20mg group (21% vs. 10%; $p < 0.05$); otherwise there were no significant differences among the groups in the distribution of adverse events with respect to involved organ system. The most common clinical adverse experiences were headache (8.8%), diarrhea (3.5%), non-specific upper respiratory infection (3.2%), nausea (2.7%) and vomiting (2.8%). The incidence of the various events were similar among the several treatment groups. Most of these events were mild or moderate in severity and few were judged to be drug-related or possibly drug-related.

There were 3 serious adverse events (all of which were judged by the investigators to be "definitely not related" to study drug). One was in the placebo arm, one in the antacid arm, and the last was in the famotidine 5 mg arm. This last patient was a 46 year old man with a history of alcoholism, anxiety, hypertension, gout, peptic ulcer disease, and esophagitis, who experienced tachycardia beginning on study day 15 and lasting for 2 days, who was subsequently diagnosed as having severe coronary artery disease.

One other patient (famotidine 10mg), a 64year old woman with a history of hypertension, was discontinued after 7 days of treatment because of weight loss and anemia. This patient entered the study with a history of hypertension for which she took pentoxifylline and nicardipine HCl prior to and during the study. The patient's weight at screening was 130.5lbs; hemoglobin/hematocrit was 11.9 g/dl / 36.2%, platelets were 178,000/mm³, and BUN and creatinine were 54 mg/dl and 1.8 mg/dl. The investigator noted the abnormal hemoglobin and BUN and creatinine as adverse events and indicated that the tests were to be repeated; 7 days later during the baseline phase the hemoglobin

was 9.9 g/dl, BUN was 47mg/dl, creatinine 1.6mg/dl, and platelets were 149,000mm³. The patient continued in the study and completed the baseline period without event and was randomized. Laboratory studies were repeated on Day 7 of the Double-Blind Phase; hemoglobin/hematocrit were 10.6 g/dl /3 1.8%, BUN and creatinine were 49 mg/dl and 1.8 mg/dl, respectively, and the platelet count was 70,000mm³. The patient's weight at this visit was 123 lbs. The patient was discontinued from the study because of "weight loss and anemia" the investigator considered "probably not" caused by the test drug. The low platelet count was not noted as an adverse event. The patient was hospitalized for "diagnostic tests". (The case report form indicates that the patient was to be sent for a barium enema). A diagnosis of systemic lupus was subsequently made. Six months later (3/27/91), after discussion with the sponsor the investigator added another adverse event, "lupus, worsened" which he judged definitely not related to the study drug; it is not clear whether the study blind had been broken at that time.

Laboratory assessments: Changes in some laboratory parameters were found. Eleven patients on famotidine (5 at 5mg, 2 at 10mg, 4 at 20mg) showed increases of 75% or more in AST (SGOT) during the study as compared to no placebo patients and 1 antacid patient. For ALT (SGPT) patients showing an increase of 75% or more were 1 placebo, 5 antacid, 6 famotidine 5mg, 3 famotidine 10mg, and 2 famotidine 20mg. None of these laboratory abnormalities was recorded as an adverse event.

One subject in the famotidine 20 mg treatment group had a finding of "WBC decreased". This subject had a history of lupus. The patient's WBC count was 3.60 x 10⁹/L, which was decreased from a pre-treatment baseline value of 5.10 x 10⁹/L. At the post-study visit on Study Day 38, the WBC count had returned to normal, 5.90 x 10⁹/L. The adverse experience was not serious.

There were no deaths of subjects in this study.

**APPEARS THIS WAY
ON ORIGINAL**

Study 019 Double -blind, placebo-controlled, dose ranging study to evaluate the efficacy of famotidine in the treatment of intermittent heartburn

Safety: Adverse Events

In this trial there were a total of 509 patients with 130 patients in the famotidine 20 mg arm with a similar number in the placebo, antacid, famotidine 10 mg arms. The most commonly involved organ systems were the nervous and psychiatric system (36 patients, 7.1%), respiratory system (34 patients, 6.7%), digestive system (25 patients, 4.9%), and musculoskeletal system (20 patients, 3.9%). There were no statistically significant differences among the treatment groups in the distribution of adverse events with regard to organ system involved. Headache and diarrhea were numerically more common in the famotidine groups than in the placebo and antacid groups; however, these numbers were small and the sponsor found no statistically significant differences among the treatment groups in the frequency of occurrence of any adverse event. No clinical adverse events were judged by the investigator to be definitely study drug related. A total of 17 patients (5 placebo, 3 antacid, 5 famotidine 10mg, and 4 famotidine 20mg) had events which were considered "possibly drug-related". These included 2 famotidine 20mg patients and 1 famotidine 10mg patient with nausea, 3 famotidine 10mg patients and one famotidine 20mg patient with diarrhea, 3 placebo patients with headache, and 3 placebo patients with constipation.

Most events were judged to be mild or moderate in severity. Only one event, in a placebo patient, was judged by the investigator to be serious.

Four patients were withdrawn from the double-blind phase prior to completion because of adverse events. One patient in the placebo group withdrew because she became pregnant. A 38 year old woman in the 10 mg group developed severe abdominal and chest pain, was found to have a large cystic pelvic mass, and was withdrawn from the study and scheduled for surgery. Two patients in the 20 mg group were withdrawn, one of which developed a moderate headache that recurred once she restarted famotidine. The other patient was a 55 year old woman who experienced dizziness and premature ventricular contractions (PVCs) during the double-blind period and was discontinued on day 15. This patient had a history of PVCs. She took two doses of famotidine during the double-blind period and developed palpitations and dizziness which lasted about 3 hours. Holter monitor showed frequent PVCs with occasional ventricular pairs but no ventricular tachycardia. Several days later the patient still complained of PVCs and was discontinued from the study and started on Lanoxin.

Laboratory assessments: Abnormal laboratory values were found but were not judged by the investigator to be serious. No patients were discontinued because of laboratory abnormalities. One subject in the famotidine 20 mg treatment group had the adverse experience of "Platelet count decreased". This subject was a 38-year-old, white male with a history of dyspepsia and intermittent sinusitis, in addition to the primary study diagnosis of intermittent heartburn. There were no abnormal findings from pre- and post-treatment physical examinations. Concomitant medication included aspirin for upper respiratory infection and rescue antacid (magaldrate) for heartburn. The patient took famotidine 20 mg intermittently during the study, from Day 2 through Day 30, for a total

of 13 days. On Study Day 30, the subject had a decreased platelet count of $120 \times 10^9/L$. The pre-treatment baseline value for this patient was $207 \times 10^9/L$. At the post-study visit on Study Day 79, the platelet count was $222 \times 10^9/L$. The decrease in platelet count on famotidine was notable, although the thrombocytopenia was not severe.

There were no deaths in the study.

Safety Summary for Heartburn Relief Trials

In general, the adverse events reported in the controlled clinical studies are consistent with the current prescription labeling for Pepcid. Side effects felt to be causally related to famotidine include headache, dizziness, diarrhea, and constipation, but these effects are usually mild. There was a patient who experienced tachycardia after 2 weeks of famotidine 5 mg daily who was found to have coronary atherosclerosis and subsequently underwent coronary artery bypass graft surgery. Laboratory abnormalities such as liver enzyme abnormalities were found in study P017 and have been reported previously. A patient was notable for having been found to have a decrease in platelet count from $178,000/mm^3$ at baseline to $70,000/mm^3$ at time of hospitalization. She was subsequently diagnosed as having systemic lupus erythematosus. One patient experienced "WBC decreased" and another experienced "platelet count decreased"; neither case was serious. One subject had "WBC count decreased" and "platelet count decreased" in the placebo arm; this case was not serious.

For the initial OTC approval of Pepcid AC the sponsor was asked to investigate the association of thrombocytopenia with famotidine use. The Sponsor calculated that as of 1993, about 6.7×10^6 person-years of exposure to famotidine tablets had occurred. It was estimated that about 1 case of thrombocytopenia occurred per 94 thousand person-years of famotidine use (assuming that all sold tablets were used, and that the famotidine dose associated was most often 20 or 40 mg daily).

D. Adequacy of Safety Testing

The safety database in the prevention clinical trials submitted in support of this OTC switch application is summarized in Table 12, which shows the numbers of patients exposed by maximum number of doses in the various treatment groups. The total number of patients exposed to famotidine 20 mg in the prevention trials was 1972. Of these, 1306 (66%) took single doses in controlled studies, and another 143 (7.3%) took four doses in the controlled study P137. In the entire safety database, 115 patients were exposed to at least 28 tablets total dose (in the use trial, over a 3 week duration; the proposed OTC label will allow 2 tablets per day for 14 days).

In the heartburn relief trials, there were another 245 patients exposed to the 20 mg tablets over a period of 4 weeks.

The present review will discuss over 490 serious adverse event reports from world-wide post marketing surveillance of famotidine, in selected body systems only. Famotidine is one of the most widely used medications in the US and world-wide. The sponsor stated that in the US since 1995, over ——— famotidine 10 mg tablets have been sold OTC.

E. Published Literature

The published clinical literature on famotidine was reviewed for the period of 31-May-1992 through 30-Jun-2002. This report updates the safety review included in the original NDA for PEPCID™ AC, which summarized the published literature for famotidine up to 31-May-1992. The Merck Worldwide Adverse Experience System (WAES) database includes adverse experience reports from the published literature and, therefore, some case reports discussed in this section overlap with the information reviewed in the Postmarketing Experience section which follows.

A search of the Merck Research Laboratories clinical literature database, using the terms “famotidine,” “toxicity,” “CNS adverse events,” “renal insufficiency,” “elderly,” and “pregnancy,” produced 870 citations. Citations from 31-May-1992 through 30-Jun-2002 were included in the general toxicity search, while all citations through 30-Jun-2002 were reviewed for CNS adverse events, renal insufficiency, and safety in elderly and pregnant patients. The following consists of some selected information from the citations by body system.

Cardiovascular

There have been reports of arrhythmias including bradycardia and heart block. The Sponsor reported that tachycardia, palpitations, and extrasystoles were reported in 3 hospitalized patients [Inman]. Another arrhythmia case [Alterman] was on famotidine 40 mg daily but was actually thought to be due to theophylline toxicity. Another case report mentioned a patient who had complete atrioventricular block and episodes of ventricular asystole occurring 5 minutes after administration of IV famotidine (dose not given). These episodes lasted up to 28 seconds and resolved on their own, and occurred on rechallenge [Schoenwald]. The famotidine prescription drug insert contains these events.

There was 1 case report of asymptomatic long QT interval in a 48 year old Japanese cirrhotic man that normalized after discontinuation of famotidine 40 mg daily. This person had also been on diuretics but had normal potassium, magnesium, and calcium levels [Endo]. Ventricular tachycardia, cardiac decompensation, and death were reported after famotidine continuous infusion at 1.7 mg/min (and multiple other medications) in a man with a history of heart disease, renal failure, and recent procainamide toxicity [O’Rangers]. The cause of the patient’s decompensation was not clear and the role of famotidine was considered uncertain.

Famotidine 40 mg was reported to reduce stroke volume and cardiac output in 3 studies [Mescheder]. A study by Welage found no effect on ejection fraction.

References

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Gastrointestinal

An observational study [Eland et al.] of post-marketing data in the Netherlands found a probable causal association between acute pancreatitis and current use of famotidine therapy, and another study of post-marketing data in Ireland [Evans et al.] could not discount the existence of such an association.

A case of gastric carcinoid tumor has been reported in the literature [Haga et al.] for a 31 year old patient without significant past or family medical history, who was on long-term therapy with famotidine (dose not reported), omeprazole, and lansoprazole. The development of gastric carcinoid tumor has been of theoretical concern for patients with chronic hypergastrinemia that may be exacerbated by long-term administration of H₂ receptor antagonists or proton pump inhibitors (e.g., in Zollinger-Ellison syndrome). However, long-term therapy is not an OTC indication.

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Hepatobiliary

Case reports of famotidine hepatic adverse events are reported in the literature [Ament; Jimenez-Saenz; Hashimoto; Sohn]. Cases of hepatitis associated with other H₂ blockers and proton pump inhibitors have also been reported in the literature. The unpredictability of acute hepatitis, the lack of a dose relationship and the absence of clinical hallmarks of hypersensitivity suggest that the mechanism involved in these cases may be an idiosyncratic reaction to a toxic metabolite [Jimenez-Saenz].

Case reports of mixed hepatocellular jaundice have been published [Ament et al.]. A case of fulminant hepatic necrosis after famotidine was given to a patient who was hepatitis B surface antigen positive can also be found in the WAES reports.

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Hematologic

Thrombocytopenia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, leukopenia, neutropenia, agranulocytosis, and granulocytopenia have been reported in observational studies and/or case reports in the literature, as discussed in the Sponsor's submission. Rare cases of agranulocytosis, pancytopenia, leukopenia, and thrombocytopenia are listed in the prescription famotidine labeling information.

Several mechanisms have been proposed in the literature to explain how H₂ receptor antagonists may induce thrombocytopenia and/or leukopenia. A case is reported of a subject in whom cimetidine and famotidine, but not a third H₂ blocker, induced thrombocytopenia [Hixson-Wallace], with clinical features suggesting a Type II cytotoxic immune reaction involving antiplatelet antibodies.

The mechanism of famotidine-induced neutropenia may involve the H₂ receptor blocking action itself, rather than any immune-mediated reaction to the drug. Liersch et al. found, in 4 patients with famotidine-induced neutropenia, a strong inhibition of the in vitro growth of granulocyte-macrophage (GM) progenitor cells during treatment. The development of GM colonies in culture was 80% reduced in comparison with a control group. The interleukin 3 and the granulocyte-macrophage colony stimulating factor-dependent growth were affected, compatible with drug-induced bone marrow failure. Full recovery of colony formation was detectable in all cultures following famotidine withdrawal. The authors also demonstrated an inhibitory effect of famotidine on normal bone marrow progenitor cells in vitro in concentrations as low as 10 mcg/mL. The absence of bone marrow eosinophilia, the block of maturation of progenitor cell at the promyelocyte stage, and the in vitro results suggest that the mechanism of neutropenia is related to the role of famotidine in blocking the H₂ receptor rather than a specific allergic reaction to the drug. The plasma concentrations of famotidine normally used in ulcer therapy are much less than 10 mcg/mL, but in a small number of patients, the progenitor cells apparently remain sensitive to the blockade of H₂ receptors. In one of the cases

reported by Liersch, even two years after discontinuation of famotidine following severe neutropenia, the growth of the patient's myeloid, erythroid, and multi-lineage progenitor cells was inhibited in vitro by famotidine concentrations of 0.5 to 5 mcg/mL. Idiosyncratic reactions may also be involved, as suggested by a case of agranulocytosis that occurred within 8 days of starting famotidine therapy [Marcus].

Consistent with the suggestion that various causative mechanisms may be involved in famotidine hematologic reactions, the literature also has reports of both neutropenia and thrombocytopenia during famotidine therapy [Oymak]. A report of TTP associated with famotidine therapy has also been documented [Kallal and Lee].

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Drug Interactions

Famotidine shows negligible interaction with the cytochrome P450 system, and therefore has little potential for interaction with drugs that are metabolized by hepatic microsomal enzymes [Humphries]. An unexpected interaction with theophylline elimination in patients with chronic obstructive pulmonary disease was reported by Dal Negro et al., in which both the elimination half-life and AUC were significantly elevated after famotidine treatment. However, no such interaction was found in a subsequent randomized, controlled, crossover study [Bachmann]. The present reviewer agrees that a significant theophylline interaction has not been identified. Antacid ingestion reduces the bioavailability of oral famotidine by 20% to 25% [Bachmann].

Lower ketoconazole levels in a renal transplant patient who was also given famotidine were considered to have led to reduced cyclosporin levels [Karlix et al.]. According to the drug insert for ketoconazole, a marked reduction in the absorption of oral ketokonazole is observed in subjects with achlorhydria, because stomach acidity is required for dissolution. An interaction of ketoconazole with cyclosporine and famotidine can result, as ketoconazole inhibits the metabolism of cyclosporin, and the ketoconazole

level is reduced when gastric acidity was reduced. Such an interaction has been reported [Karlix et al.].

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F. Worldwide Post-Marketing Surveillance

Over _____ prescriptions for oral famotidine have been dispensed in the United States from 1993 through 31-December 2001, and over _____ famotidine 10-mg tablets (film-coated, chewable, gelcap, and famotidine/antacid combination tablets) have been sold OTC in the United States since marketing approval (see Table 27). The Sponsor estimated that there have been 186 million OTC users of famotidine through June 23, 2002 (PEPCID™ AC/PEPCID™ COMPLETE/Private Label Famotidine, based on courses of therapy of 2 tablets per day for 14 days). The 20mg and 40 mg tablet formulations were approved in 1986 (see Table 2 and Table 3), and the 10 mg formulation was approved in 1995 (see Table 1).

Table 27 Marketing data from submissions of 22 November 2002 and 30 June 2003

Number of Famotidine Tablets, RAPITABS, Chewable Tablets, Gelcaps, and Oral Suspension Distributed in the US Market Introduction to 31-May-2003	
Famotidine Dosage Strength	Product Distributed
10-mg tablet, chewable tablet, gelcap	
20-mg tablet and RAPITAB	
40-mg tablet and RAPITAB	
Oral suspension (40 mg/5 ml)	

The Prescription Famotidine information is from Intercontinental Marketing Services (IMS) Health and is the number of prescriptions in the USA from 1993 through 2001. Data for prescriptions other than retail is estimated for 1993-1996 based on 1997-2001 averages. The OTC data are from Information Resource, Inc. (IRI) and give the retail sales in the USA from 1995 through June, 2002. Retail OTC tablet sales for _____ were estimated by the Sponsor for 2001 and 2002 year-to-date. An average of _____ prescriptions were written per year over the nine-year interval shown. The number of prescriptions per year was highly stable. Likewise the rate of OTC retail sales has been quite stable over the 6.5-year period 1996 to mid-2002, at an average of _____ tablets sold per year.

These stability of sales allow a rough comparison of the number of OTC

Table 27a
Prescription Famotidine

Source: IMS Health

Year	Prescriptions
1993	
1994	
1995	
1996	
1997	
1998	
1999	
2000	
2001	

Table 27b
Over-the Counter (OTC) Famotidine

Source: IRI

Year	Tablets Sold at Retail
1995	
1996	
1997	
1998	
1999	
2000	
2001*	
2002 YTD (thru 6/23/02)*	

famotidine courses versus prescriptions of famotidine.

The FDA requested **serious adverse event (SAE)** reports from the sponsor WAES database, consisting of MedWatch reports from the USA and Council for International Organizations of Medical Sciences (CIOMS) reports from other countries, over the time span from 1987 to mid-2002, involving the following body systems: hematologic and lymphatic, hepatobiliary, nervous system and psychiatric, and renal and urinary systems. These reports were evaluated by the reviewer according to the criteria in Table 28.

Table 28. Causality rating terms

Causality Rating	Explanation
Not related	clearly related to factors other than subject drug, such as the subject's clinical state, therapeutic interventions, or concomitant medications
Unlikely	most likely produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications, and does not follow a known response pattern to the subject drug
Possible	follows a reasonable temporal sequence from the time of drug administration; and/or follows a response pattern known to the subject drug; but could have been explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications
Probable	follows a reasonable temporal sequence from the time of drug administration; and follows a response pattern known to the subject drug; and unlikely to be explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications
Highly probable	follows a reasonable temporal sequence from the time of drug administration; and follows a response pattern known to the subject drug; and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant medications: rechallenge is positive

For the body systems requested, the sponsor provided a total of 572 WAES reports of SAEs that were submitted by health professionals, of which there were a total of 513 unique reports, as some reports were submitted under more than one body system. The reviewer evaluated all these reports and found that a total of 492 WAES reports had at least one AE term rated as possible or probable in causality. This high proportion of reports with possible or higher probability is not surprising, since the reports were SAEs submitted by health professionals. The Appendix C gives a list of the WAES report numbers where at least one event was evaluated by the reviewer as possible or probable.

At issue for the present submission is the safety of 20 mg famotidine tablets (b.i.d. for up to 14 days) under OTC marketing conditions. This 20 mg dose is available OTC only in Australia, but not in the USA or Japan or other markets. A smaller dose (10 mg famotidine tablets, b.i.d for up to 14 days) has been available OTC in the USA since 1995.

The vast majority of the post-marketing experience reports pertain to prescription famotidine. Oral famotidine is often prescribed to hospitalized and/or critically ill patients, and it is also often prescribed for prophylactic and/or long-term use. Both of these circumstances would not apply to the OTC marketplace. In addition, famotidine is often used by people over the age of 50 years, and many of these users are on numerous concomitant medications. All of these factors complicate the use of post-marketing data to evaluate safety of 20 mg famotidine tablets for OTC marketing. Needless to say, the usual difficulties associated with post-marketing surveillance also apply, such as under-reporting (which hinders estimation of the incidence rate

of AEs) and the uncontrolled clinical setting (which complicates attribution of causality, because an AE may be caused by concomitant medications or an underlying medical condition).

The present reviewer performed the following specific analyses in order to account for these issues. To begin with, the WAES reports were re-classified by total daily dose of oral famotidine taken, and not by actual tablet formulation taken. This is because a daily dose of 20 mg famotidine (10 mg tablets b.i.d.) is already available OTC, and the present application would make a daily dose of 40 mg available OTC (20 mg tablets b.i.d.). Hence the principal safety issue is whether available post-marketing experience reveals any potentially increased risk at the higher daily dose. If a subject received more than one oral daily dose during the course of therapy, the report was classified under the highest daily dose.

Table 29 WAES reports of SAEs

SAE cases, at least one event possible or probable causality	All doses* (N=492)	10 mg daily dose (N=22)	20 mg daily dose (N=114)	40 mg daily dose (N=254)
Subject was an outpatient	282	18	67	131
Subject used drug 14 days or less before drug discontinued because of SAE	117	6	28	68
Subject had hematologic† SAE	228	12	53	123
Subject had hematologic† SAE and died	34	3	9	16
Subject had neurologic or psychiatric SAE‡	111	5	17	56
Subject had neurologic or psychiatric SAE and died	4	0	0	1
Subject had hepatobiliary SAE‡	85	1	36	38
Subject had hepatobiliary SAE and died	6	0	2	3
* All doses totals include the 10 mg, 20 mg, and 40 mg daily doses as well as other doses and unknown doses.				
† Included were any of the following: leukopenia, agranulocytosis, neutropenia, granulocytopenia, bone marrow depression, aplastic anemia, or thrombocytopenia				
‡ Terms classified by Sponsor				

The reviewer also evaluated each WAES report for the medical history, the time sequence of famotidine administration in view of the clinical course, and the time sequence of any concomitant medications. Analyses were restricted to the 492 WAES reports with at least one AE term rated as 'possible' or 'probable' by the criteria of Table 28. The clinical course of one patient is submitted as one report; a report may have many AE terms. The numbers of SAE reports in various body systems, for different daily doses, is given in Table 29 including only the possible/probable reports. However, all submitted WAES reports in which a death occurred, including reports where the death event was rated as unlikely or not related, are included below in Table 30.

Table 29 shows that the number of reported SAEs is consistently more than a factor of two greater at the 40 mg daily dose than at the 20 mg daily dose, for both the entire group of 492 possible/probable WAES reports and for several subsets (except hepatobiliary). In the entire group there were 254 serious reports at 40 mg/day, versus 114 at 20 mg/day. The reviewer notes

that the median age of subjects in these reports is 63 years, and that many of them were critically ill and on multiple medications. An analysis was performed to determine whether subjects were hospital inpatients or outpatients when they began their famotidine course. When the hospital inpatients are excluded, an excess of serious reports is found at the higher daily dose. A total of 282 possible/probable reports involved subjects who were outpatients when they began their famotidine course (the total of possible/probable reports for hospitalized patients was 152). For the others, the status could not be determined. For outpatients with SAEs, there were 131 SAE reports involving the 40 mg daily dose versus 67 SAE reports at the 20 mg daily dose. Moreover, famotidine is often prescribed prophylactically and used chronically, whereas OTC users should not take continuous courses longer than 14 days. When long-term users are excluded, Table 29 shows that 117 possible/probable SAE reports involved subjects who used famotidine for 14 days or less before the drug was discontinued because of the SAE. In this subset of the database, there were 68 SAE reports involving the 40 mg daily dose versus 28 SAE reports at the 20 mg daily dose.

Table 29 also compares the numbers of possible/probable SAE reports involving various body systems at the different daily doses. Again, for the hematologic and neurologic/psychiatric systems, there are two to three times as many reports at the 40 mg daily dose as there are at the 20 mg dose. However, the numbers of hepatobiliary reports are more similar, with 38 reports at 40 mg daily dose versus 36 reports at 20 mg/day. The subjects with hematologic SAEs were the most likely to have a fatal outcome.

Table 30. Deaths in Submitted WAES reports (N=57 deaths*)

WAES number	Daily Dose mg	Principal Terms	Highest Causality	Concomitants	Note
WAES 00120421	40	PANCYTOPENIA, PNEUMONIA NOS	unlikely	allopurinol, methotrexate	rheumatoid arthritis; chronic renal failure; filgrastim; pancytopenia recovered but patient died from pneumonia
WAES 01020683	40	THROMBOCYTOPENIA, COMA HEPATIC	possible	fosfomycin; lasix	hepatitis B, cirrhosis
WAES 0202USA01966	40	AGRANULOCYTOSIS	probable	verapamil, pantoprazole	renal failure, History nephrectomy
WAES 0304USA01607	40	PANCYTOPENIA, APLASTIC ANAEMIA	possible	aprindine HCl; not on chemotherapy	The course of events (leukopenia>agranulocytosis>thrombocytopenia) suggests drug induced aplastic anemia. Famotidine is regarded as the most likely cause of the adverse event
WAES 86040732*	40	HALLUCINATION NOS, CONFUSION	possible	ludiomil, morphine, cocaine	cervical cancer
WAES 86040737	40	THROMBOCYTOPENIA, LEUKOPENIA NOS	possible	sucralfate, cimetidine, metoclopramide	Death from GI bleed.
WAES 88020755	40	THROMBOCYTOPENIA	possible	carafate	
WAES 88050012	40	PANCYTOPENIA SHOCK	possible	indocin, micronase	diabetic alcoholic w/ulcer temporal arteritis Blood cultures positive for staph aureus
WAES 88050390	40	ANURIA, NEUTROPENIA	possible	sinemet, amantadine, citicoline	Septic shock. History of Parkinson's.

WAES number	Daily Dose mg	Principal Terms	Highest Causality	Concomitants	Note
WAES 88080392	40	HEPATIC FAILURE, COMA HEPATIC	possible	Levomopromazine, promazine, valerian, digitoxin	Chronic obstructive bronchitis, Congestive heart failure, diabetes
WAES 89080641	40	HEPATIC CIRRHOSIS, RENAL FAILURE NOS	possible	furosemide, spironolactone, acetyldigoxin, sotalol	Physician attributed worsening cirrhosis to famotidine. Alcoholic. History of hepatitis B, heart failure
WAES 89090148	40	PANCYTOPENIA	possible	glyburide meprobamate/quinine melperone	Event abated after use stopped. Diabetic. Pancreatic cancer bone marrow biopsy.
WAES 90010777	40	HEPATIC NECROSIS	possible	none	History of hepatitis B SA positive
WAES 90060292	40	BONE MARROW DEPRESSION SEPTIC SHOCK	possible	lorazepam	alcoholic; non-Hodgkin's lymphoma; sarcoidosis, portocaval shunt. Renal failure
WAES 93121150	40	AGRANULOCYTOSIS, ANAEMIA NOS	possible	glibenclamide (glyburide)	pancytopenia. diabetes. Hepatic disorder. Cardiac failure; History drug allergy, chronic urticaria
WAES 94051343	40	THROMBOCYTOPENIA, CARDIORESPIRATORY ARREST	possible	amiodarone, enalapril, cipro, omeprazole, persantine, vancomycin	end stage renal disease, cardiomyopathy hypertension
WAES 94060865	40	LEUKOPENIA NOS PNEUMONIA	possible	erythrocin nifedipine sparfloracin	
WAES 95056081	40	SHOCK COAGULOPATHY			small intestine infarction
WAES 95111539	40	NEUTROPENIA	possible	Prednisolone antacids alfacalcidol	polymyositis
WAES 96052151	40	MYELOSUPPRESSION SKIN ERUPTION	probable	sucralfate	cause of death was sepsis also received IV famotidine
WAES 96061008	40	PANCYTOPENIA	possible	zonisamide; cisapride	"pancytopenia was a major cause of death" respiratory failure and renal failure also contributed. No autopsy. Famotidine strongly suspected but zonisamide given at same time.
WAES 97051979	40	CARDIO-RESPIRATORY ARREST, MULTI-ORGAN FAILURE	unlikely	diltiazem hcl, teprenone	serum concentration of famotidine was 28.8 ng/ml.
WAES 98012543	40	PANCYTOPENIA	possible	tegafur	rectal cancer. MD felt pancytopenia was "probably" related to therapy with famotidine.
WAES 98085518	40	STEVENS JOHNSON SYNDROME, RENAL IMPAIRMENT NOS	unlikely	furosemide, spironolactone	Polymyalgia rheumatica. Renal insufficiency
WAES 98100039	40	ACIDOSIS HYPERCHLOREMIC, RENAL FAILURE NOS	possible	enalapril, furosemide	Event abated after use stopped. methicillin resistant staph aureus infection
WAES 00122242	20	APLASTIC ANAEMIA, PNEUMONIA	possible	allopurinol, isosorbide dinitrate; spironolactone, lasix	abated after use stopped; G-CSF; died from pneumonia; WBC count recovered
WAES 01100646*	20	THROMBOCYTOPENIA, PNEUMONITIS	possible	levofloxacin	systemic lupus erythematosus Sjogren's

WAES number	Daily Dose mg	Principal Terms	Highest Causality	Concomitants	Note
WAES 0204USA01458	20	PANCYTOPENIA, RENAL FAILURE ACUTE CONVULSION	probable	allopurinol, minocycline, cilastatin, cefozopram, imipenem; lasix, enalapril	history of chronic renal failure creatinine 3.47mg/dl; also given IV; hospitalized with pneumonia dechallenge, rechallenge
WAES 0206USA01643*	20	CARDIO-RESPIRATORY ARREST, VENTRICULAR FIBRILLATION	unlikely	losartan	Physician said 'almost unthinkable'
WAES 0212USA00620	20	DYSKINESIA, DISSEMINATED INTRAVASCULAR COAGULATION	possible	nifedipine, zopiclone, isosorbide dinitrate	history of renal failure, myelodysplastic syndrome, hepatic damage. CNS symptoms resolved after discontinuation of famotidine
WAES 87060466	20	HYPERSENSITIVITY NOS, CARDIO-RESPIRATORY ARREST	possible	Artane, Dyazide Neosporin	
WAES 88060294*	20	CONVULSIONS NOS, ENCEPHALITIS	unlikely		herpes encephalitis
WAES 90060713	20	PANCYTOPENIA	possible	none	
WAES 92090513	20	APLASTIC ANAEMIA, DISSEMINATED INTRAVASCULAR COAGULATION	possible	ofloxacin benproperines cefoperazone	lupus
WAES 95120670	20	THROMBOCYTOPENIA MYOCARDIAL INFARCTION	possible	cefmetazole, rebamipide, ceftazidime	Bloody stools
WAES 96126147*	20	HEPATIC FUNCTION ABNORMAL NOS	probable	antibiotics, furosemide	Event abated after use stopped. Diabetes, renal insufficiency
WAES 98012545	20	PNEUMONIA NOS, AGRANULOCYTOSIS	possible	imipenem cilastatin cimetidine sodium bufferin vasotec amiodarone	CHF hepatitis C cerebral infarction DM
WAES 99041000	20	THROMBOCYTOPENIA, LEUKOPENIA NOS	possible	pranoprofen azosemide	Glomerulonephritis. Hepatic disorder
WAES 99100858	20	HEPATIC FUNCTION ABNORMAL NOS, JAUNDICE NOS	possible	voglibose, pravastatin	Diabetes, hepatic disorder
WAES 99120864*	20	THROMBOCYTOPENIA, RENAL IMPAIRMENT NOS	possible	lasix amlodipine vancomycin	Renal impairment. creatinine 7.3 mg/dl Hepatic disorder Death attributed to renal insufficiency
WAES 00081202	10	AGRANULOCYTOSIS, PNEUMONIA NOS	possible	allopurinol, amlodipine; lasix lansoprazole	chronic renal failure; CHF;
WAES 0303USA01690	10	PANCYTOPENIA, DISSEMINATED INTRAVASCULAR COAGULATION	possible	ginger (+) ginseng (+) maltose (+) zanthoxylum fruit (DAIKEN-CHUTO)	bone marrow biopsy on _____, drug-induced pancytopenia due to Daiken-Chuto or famotidine; physician reported therapy with famotidine more likely "responsible". Cause of death was pancytopenia. No chemotherapy
WAES 89020156	10	BONE MARROW DEPRESSION NOS, PANCYTOPENIA	possible	Haldol prednisone	Renal failure; creatinine 4.4 mg/dl; vasculitis

WAES number	Daily Dose mg	Principal Terms	Highest Causality	Concomitants	Note
WAES 00064586	unkn	ENCEPHALOPATHY NOS, HEPATITIS NOS	possible	losartan	pneumonia and respiratory insufficiency
WAES 00072328	unkn	SEPSIS, DISSEMINATED INTRAVASCULAR COAGULATION	possible	cefazolin, heparin, verapamil	Multiple IV line infections. Pulmonary hypertension. Subdural hematoma.
WAES 01012379	unkn	HEPATIC DISORDER NOS, HEPATITIS NOS	possible	ranitidine, teprenone, metoclopramide,	Still's disease
WAES 01041721	unkn	THROMBOCYTOPENIA, ACUTE RENAL FAILURE	possible	loxoprofen heparin, ceftazidime	acute renal failure
WAES 01080306	unkn	GRANULOCYTOPENIA, DISSEMINATED INTRAVASCULAR COAGULATION	possible	piperacillin minicycline clindamycin imipenem	microscopic polyangiitis; vasculitis
WAES 01112446*	unkn	NEPHRITIS INTERSTITIAL, ERYTHRODERMA	possible	amlodipine, warfarin, ticlodipine, furosemide	Abated after use stopped. Erythroderma attributed to amlodipine, death to dehydration. history of HTLV-1 antibody positive, B cell lymphoma in the lung
WAES 0112USA02368	unkn	STEVENS JOHNSON SYNDROME, DISSEMINATED INTRAVASCULAR COAGULATION	possible	cefcapene aspirin diclofenac	Methicillin resistant staph aureus
WAES 0206USA01656	unkn	PANCYTOPENIA	possible		abated after use stopped. Systemic sclerosis; Raynaud's; secondary amyloidosis cardiac and renal failure
WAES 90021129	unkn	BACTERIAL SEPSIS, JAUNDICE NOS	unlikely	captopril, furosemide, metildigoxine, isosorbide	MI, cardiomyopathy
WAES 92095544	unkn	BONE MARROW DEPRESSION NOS, NEUTROPENIA	probable	antibiotic	cardiac and renal failure
WAES 92095548	unkn	BONE MARROW DEPRESSION NOS, AGRANULOCYTOSIS	possible	antibiotic	
WAES 92127270	unkn	INTERACTION WITH WARFARIN, SUBDURAL HEMATOMA	See comment Appendix D		artificial heart valve surgery
WAES 93020031	unkn	APLASTIC ANAEMIA, HEPATITIS	possible	cimetidine, sulfamicillin	rash
WAES 93071004*	unkn	CHOLESTATIC SUICIDE	See comment Appendix D	nortriptyline	suicide attempt

* Asterisk indicates death event evaluated as unlikely or not related

A summary of all deaths in the submitted WAES reports is in Table 30, which includes the deaths in the body system groups noted in Table 29. An asterisk by the WAES number indicates that the death was evaluated as unlikely or not related to famotidine by this reviewer, but not necessarily the health care provider who submitted the report. The "highest causality" shown in Table 30 is that of the AE term with the most likely causality rating. Up to three AE terms for any report are shown in Table 30, including the term with the most likely causality rating. Of the 57 WAES reports involving deaths, the greatest number involved a daily dose of 40 mg (25 deaths), versus a total of 15 deaths involving a daily dose of 20 mg (and 3 deaths involving a daily dose of 10 mg). Appendix D has narratives of the death reports.

Five WAES reports were retrieved by the Sponsor for QT prolongation. One of the cases was most likely caused by a nortriptyline overdose. Three of the reports of QT prolongation involved Torsade de pointes. These cases are not clearcut because of underlying medical conditions and concomitant medications. One of them was confounded by possible electrolyte imbalances and a cranial lesion, while another case involved a concomitant drug that could affect QT intervals and a diuretic. In the last case the QT prolongation resolved while the patient was continued on famotidine (Appendix E).

Twelve WAES SAE reports were retrieved for rhabdomyolysis (9 from Japan, 2 from France, 1 from Germany).

Reports of pancreatitis were found in the Merck WAES Post-Marketing Database.

A case of fulminant hepatic necrosis after famotidine was given to a patient who was hepatitis B surface antigen positive can also be found in the WAES SAE reports.

Single case reports involving possible interactions with digoxin, dilantin, midazolam, nortriptyline, theophylline, and warfarin were included in the WAES SAE reports provided by the Sponsor. Dilantin, theophylline and warfarin were previously studied in man with no significant effects found according to the drug insert. None of the cases was conclusive.

Discussion. The WAES reports in the body systems requested by the FDA were submitted from many countries, with the greatest number of reports coming from Japan, followed by the USA and then by Germany (see Table 31). In each of these countries, which collectively account for 91% of the possible/probable reports, the same trend can be seen, that the greatest number of SAEs is reported involving a daily dose of 40 mg versus daily doses of 20 mg or 10 mg. Since this same trend is found in:

- all WAES reports with at least one SAE rated as possible or probable;
- subsets thereof selected to exclude hospitalized subjects at the start of the famotidine course and subjects who used famotidine longer than 14 days;
- subsets thereof defined by body system;
- all WAES reports with fatal outcomes;
- all WAES reports with at least one SAE rated as possible or probable, from each of the three different countries that contribute nearly all of the reports;

it is concluded that the trend is statistically robust and not confounded by under-reporting biases in post-marketing surveillance.

Table 31. SAE reports by country of origin

SAE cases, at least one event possible or probable causality	All doses* (N=492)	10 mg daily dose (N=22)	20 mg daily dose (N=114)	40 mg daily dose (N=254)
Japan	294	16	91	151
USA	124	5	16	59
Germany	30	0	1	18

When this trend is combined with the distribution and prescription data supplied by the Sponsor, it appears that the 40 mg daily dose is associated with an increased risk of an SAE report when compared to the 20 mg daily dose. In the USA, about ~~as many~~ as many 20 mg tablets are sold as 40 mg tablets (see Table 27), but the numbers of prescriptions at the higher versus lower daily dose are not well determined.

A similar analysis was performed using the FDA AERS database by HFD-430; reference is made to the memorandum of Lauren Lee, dated July 31, 2003, for serious hematological adverse events from 1987 through 1994 (date chosen to exclude OTC famotidine). The search retrieved 37 SAE reports, of which 70% involved patients at a daily dose of 40 mg and 11% involved patients at a daily dose of 20 mg. These reports include 16 deaths, 9 of which involved the 40 mg daily dose. However, the post-marketing data are not designed to measure a dose response effect, and controlled clinical study data may be better suited to do so.

Although post-marketing reports were obtained from many countries worldwide, distribution and prescription data for famotidine is available only for the USA (see above). Based upon this information, it is possible to make some estimates of the incidence of famotidine SAE reports from the post-marketing data, in the selected body systems (hematologic, neurological and psychiatric, hepatobiliary, renal and urinary). Information is not available to relate the incidence of SAE *reports* to that of actual serious *events* because of under-reporting. However, it is generally accepted that in post-marketing surveillance, serious adverse events may be under-reported by an order of magnitude.

The Sponsor's submission estimated that 186 million OTC famotidine courses have been taken in the USA since market introduction, assuming 28 tablets per drug course. An estimate can now be made of the incidence of SAE reports per US OTC famotidine course. In the WAES SAE reports, the total number of reports was found in which

- the daily dose was 10 mg (total 5 reports from USA, possible or probable),
- the daily dose was 20 mg *excluding* reports where the formulation taken was the 20 mg tablet (total 8 reports from USA, possible or probable).

These reports were assumed to involve OTC users who could take 10 mg famotidine once or twice a day, as well as possibly some users who were prescribed OTC daily doses. Subjects known to have taken prescription famotidine at the OTC daily dose were excluded. Also excluded were reports involving subjects who took the 10 mg tablet but for whom the total daily dose was not given. In the WAES database of reports with at least one possible or probable event, there were a total of 13 reports from the USA satisfying the two conditions above (9 neurological/psychiatric and 4 hematologic SAEs). Hence, the number of SAE reports possibly or probably associated with famotidine, in US OTC users, was at least 5, and up to 13, in the selected body systems. So the incidence of SAE *reports* in these body systems is estimated as at least 1 per 37 million OTC drug courses, up to 1 per 14 million OTC drug courses. It is not known how many drug courses would be taken per year by a typical OTC consumer.

Similarly, the Sponsor's submission estimated that about ~~prescriptions~~ prescriptions were dispensed from 1993 through 2001. In the WAES database of reports with at least one possible or probable event in selected body systems, there were a total of 75 SAE reports within this period from the USA, of which 9 met the criteria above to be considered OTC users. Therefore there were 66 reports involving prescription users in the USA, and the incidence of SAE *reports*

possibly or probably associated with famotidine in the selected body systems is estimated as 1 per _____ prescriptions.

In conclusion, the worldwide post-marketing surveillance data, using adverse event reports from the Sponsor's WAES database, indicate an increased number of SAE reports or deaths at a 40 mg daily dose versus a 20 mg daily dose. These SAE reports were submitted by health professionals, and were further evaluated by the reviewer as to clinical course, time history of medications, and concomitant medications. A similar conclusion was reached by an HFD-430 analysis of FDA AERS data from the USA, which found an increased number of hematologic SAE reports or deaths at 40 mg daily dose versus 20 mg daily dose. It is noted that post-marketing data are not well suited to measure a dose-response effect. It is also noted that the incidence of SAE reports from the USA is low: at least 1 per 37 million OTC drug courses, up to 1 per 14 million OTC drug courses; also, 1 per 1.1 million prescriptions (20 mg and 40 mg doses as well as other non-OTC doses, combined). However, no information is available to determine the extent of under-reporting in post-marketing surveillance of famotidine, and use data are not available to determine person-years of exposure.

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VIII. Dosing, Regimen, and Administration Issues

See section IX for dose reduction in elderly patients, and see Section VII E for discussion of interaction with ketoconazole and cyclosporine.

IX. Use in Special Populations

A. Review of Famotidine Association with Neuropsychiatric Adverse Events and Age of Subjects

Renal excretion is the primary route of elimination of famotidine, and clearance of famotidine is delayed in patients with impaired renal function. A study of famotidine pharmacokinetics in 31 subjects [Takabatake T, Ohta H, Maekawa M, et al. 1985] found that renal impairment, as measured by creatinine clearance (CrCl), was strongly correlated to slower elimination of famotidine. The authors recommended a 50% dose reduction for those with moderate impairment (CrCl of 30-60 mL/min/1.48m²) and a 75% dose reduction for severe impairment (CrCl <30 mL/min/1.48m²). Likewise Gladziwa et al. 1988 studied 22 subjects with renal failure and observed a 7- to 10-fold increase in the elimination half-life as compared to normal subjects; they recommended a dose reduction to 1/3 of normal in the case of renal failure.

Famotidine crosses the blood-brain barrier and is measurable in the cerebrospinal fluid (CSF) [Kagevi et al. 1987]. As histamine H₂ receptor antagonists inhibit specific histamine receptors in the cerebral and hippocampal cortices [Ruat et al], the presence of famotidine in the CSF may produce psychotropic effects. There are case reports in the literature of neuropsychiatric events, including confusion, delirium, disorientation and hallucinations, associated with use of famotidine. Dickinson et al. 1986 reported a case of confusion in a trial of 63 patients of median age 73; Rodrigo et al. 1989 reported one case of delusion in a trial of 51 patients on 40 mg famotidine per night. Rodgers and Brengel described oral famotidine-associated mental status changes (confusion, disorientation and hallucinations) in a 77 year old who underwent discontinuation and rechallenge. There are also 2 reports of CNS reactions (such as disorientation and convulsions) in hemodialyzed patients on intravenous famotidine whose CSF levels of famotidine were elevated by factors of 3 to 4 above those in other hemodialyzed patients who did not experience CNS reactions [Yoshimoto et al]. Odeh and Oliven described central nervous system reactions (confusion, agitation, disorientation) associated with famotidine at 40 mg/day in five elderly subjects (61 to 85 yr) of whom 4 had renal failure of varying severity. These reactions developed up to a few days after initiation of therapy and resolved within 48 hours after discontinuation.

There are no controlled clinical trials that establish the incidences of CNS adverse events or that have measured increased risks in special populations. However, the incidences are low. In a review of famotidine safety [Howden and Tytgat] a meta-analysis of 27 clinical trials found serious nervous system or psychiatric adverse events reported in 14/6938 patients (0.2%) in postmarketing studies, 89/5458 (1.6%) in local postmarketing studies, and 43/49692 patients (0.09%) in surveillance studies. The rate of spontaneous reports to the FDA SRS involving neuropsychiatric events was also

provided by the Sponsor for the first 3 years after famotidine approval: there were 47 reports of confusion, 35 reports of headache, and 28 reports of hallucinations, for an estimated rate of 26 reports per million prescriptions [Juergens]. In the WAES database of postmarketing surveillance reports to the sponsor, there are 130 patients who suffered serious nervous system or psychiatric events reported by medical professionals. The median age of these patients was 63 years, so at a minimum, half of the reports involved senior citizens.

Cantu reported that advanced age is a risk factor for central nervous system reactions in those who use H₂ receptor blockers. Fifty-nine percent (59%) of H₂ blocker-associated CNS spontaneous reports to the FDA involved patients above the age of 60. This is similar to the age distribution for the nervous system and psychiatric serious adverse events in the WAES database as discussed above.

Since patients with impaired renal function, among which are many elderly, can have markedly reduced rates of famotidine elimination, the risks of CNS and other adverse events may be increased in such patients. It is appropriate for patients with moderately reduced creatinine clearance (<60 mL/min/1.48m²) to reduce the dose by 50%, since the AUC at equal doses is approximately twice that in normal patients [Takabatake]. Similarly, the published pharmacokinetic data of Echizen and Ishizaki 1991 show that famotidine clearance decreases by about a factor of two above the age of sixty in a normal population. Also, Lin et al. 1988 found that the famotidine clearance was 50% less in a healthy elderly group (65 to 74 years; 0.19 L/h/kg) than in a young group (23 to 32 yrs; 0.39 L/h/kg). Lin et al 1988 also showed that the elimination half life was prolonged (at 4.1 hr) in the elderly group compared to that in the young group (2.9 hr).

The elderly group in the Lin et al. 1988 study was healthy and had a creatinine clearance not significantly different from that of normal young subjects, whereas an elderly group with health problems is likely to have a lower creatinine clearance. Burkhardt et al. 2002 assessed the renal function of a series of 30 elderly subjects. Of these 30 subjects, 16 were hypertensives and 9 had diabetes, possibly a more representative population than in the Lin et al. study. The Burkhardt et al. and Lin et al. elderly groups were similar in terms of mean age (74.5 vs. 69 yrs) and mean weight (66.7kg vs. 76.2kg). However, the Burkhardt et al. elderly patients had a mean creatinine clearance (measured) of 57.1 mL/min, just under half of the measured creatinine clearance of the Lin et al. group. Since famotidine elimination occurs primarily by renal tubular secretion, the famotidine clearance of an elderly population with health problems like that of Burkhardt et al. would be reduced even more than that of the Lin et al. healthy elderly group, which was already reduced compared to that in the young group.

In summary, the literature supports the current prescription labeling information, which recommends famotidine dosage reduction by half for those subjects with moderate as well as severe renal insufficiency. Prompted by a letter from Dr. _____ on June 16, 2000, the Agency recommended a change in the prescription labeling for Pepcid to reflect the need for dosage adjustment in patients with moderate or severe renal impairment. The label now reads

"In adult patients with moderate (creatinine clearance <50 mL/min) or severe (creatinine clearance <10 mL/min) renal insufficiency, the elimination half-life of PEPCID is

increased. For patients with severe renal insufficiency, it may exceed 20 hours, reaching approximately 24 hours in anuric patients. Since CNS adverse effects have been reported in patients with moderate and severe renal insufficiency, to avoid excess accumulation of the drug in patients with moderate or severe renal insufficiency, the dose of PEPCID may be reduced to half the dose or the dosing interval may be prolonged to 36-48 hours as indicated by the patient's clinical response."

However, in an OTC setting, creatinine clearance values will not be available to consumers who self-medicate. Moreover, in elderly patients the creatinine clearance can be overestimated from apparently normal BUN and creatinine values, because of decreased muscle mass. Many elderly people have silent renal insufficiency and may not be aware, or have never been told, that they have reduced renal function. An alternative method is needed to guide OTC consumers, using a surrogate marker that is easily understood, generally available, and reasonably well correlated with creatinine clearance. In this instance, age is the obvious marker. _____

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B. Evaluate Pediatric Program

Not applicable.

C. Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy.

See Section IX. A.

X. Conclusions and Recommendations

A. Conclusions

The stated rationale for OTC switch of famotidine 20mg is to provide increased efficacy for prevention and/or relief of heartburn, when compared to famotidine 10 mg which is currently available OTC. In the present submission, the pharmacodynamic study P118 found that famotidine 20 mg produces higher gastric pH measurements than the 10-mg dose. The sponsor notes that a direct correlation between gastric pH and heartburn severity has not been established, but suggests that the 20-mg dose will be more effective in preventing/attenuating intermittent heartburn. The sponsor states, "In studies supporting the current application that included both famotidine 10-mg and famotidine 20-mg dose groups, there is a clear directional trend, in some cases statistically significant, favoring 20 mg over 10 mg for the treatment and prevention of heartburn". It is interesting that study P118 did not find any statistically significant difference between famotidine 20 mg and famotidine 10 mg in terms of number of reflux episodes or increase of intra-esophageal pH. Refer to the complete efficacy review by Dr Lopez which is pending.

Hence, on the benefit side of a risk-benefit trade, there is pharmacodynamic evidence and a "directional trend" in clinical studies that is "in some cases statistically significant", according to the Sponsor. However, on the risk side there are increased safety concerns for the higher total daily dose. The present reviewer feels that in order to achieve a favorable risk-benefit ratio for an OTC switch of the higher dose formulation, the safety profile should be comparable to that of the lower dose formulation that is already marketed OTC. Moreover, the safety profile for a drug as widely used as famotidine should include not only the frequencies of the common AEs experienced by more than 1% of users, but also the relatively rare, potentially serious AEs. If the higher dose formulation has a similar safety profile for common AEs, but is associated with a greater frequency of rare but serious AEs, then the risk-benefit ratio for treating a condition as unserious as occasional heartburn is unfavorable for an OTC switch.

The safety database provided by the sponsor for famotidine 20 mg included subjects of 6 "heartburn prevention or supportive" trials in both OTC and controlled clinical settings. However, the majority of the subjects evaluable for safety took only one dose, and only 115 subjects were exposed to at least 28 doses, the number of doses permitted in continuous use by the proposed OTC label before a doctor should be consulted. In the two "heartburn relief" clinical trials, an additional 245 subjects were given 20 mg famotidine tablets. Safety data from both the prevention and the relief trials were supportive of safety, but these trials were able to reveal only common side effects. During these trials, the sponsor identified 1 case each of decreased WBC count and platelets in the famotidine arms. The reviewer also identified one additional case of thrombocytopenia (platelet count of 70,000) in Study 017. The present reviewer agrees that the common side effects are generally mild and similar in frequency for famotidine 20 mg and famotidine 10 mg. The common side effects include headache, constipation, diarrhea, and dizziness.

The Sponsor submitted line listings and numbers of adverse event reports submitted by health care professionals from its Worldwide Adverse Event System database. Upon review, the Agency requested copies of the SAE reports with narrative summaries in the following body systems: hematologic, neurological and psychiatric, hepatobiliary, renal and urinary systems. These reports indicate an increased number of SAE reports or deaths at a 40 mg daily dose versus a 20 mg daily dose. A total of 492 famotidine SAE reports were evaluated as having at least one event rated as possible or probable causality. In that dataset, as well as subsets that excluded hospital in-patients and chronic users, and in all deaths from the WAES database in the selected body systems (57 deaths), there were more serious adverse events and deaths at 40 mg daily dose than at 20 mg daily dose. Similarly, an HFD-430 analysis of FDA AERS data from the USA found increased numbers of hematologic SAE reports or deaths at 40 mg daily dose versus 20 mg daily dose. It is noted that post-marketing data are not well suited to measure a dose-response effect. It is also noted that the incidence of these SAE reports from the USA is low: at least 1 per 37 million OTC drug courses, up to 1 per 14 million OTC drug courses; also, 1 per 1.1 million prescriptions (20 mg and 40 mg strength tablets as well as other non-OTC doses, combined). However, no information is available to determine the extent of under-reporting in post-marketing surveillance of famotidine.

If the present application were approved, the 40 mg daily dose would become available OTC, whereas only the 20 mg daily dose is now available OTC (in the form of 10 mg tablets taken twice a day). Since the post-marketing data indicate a higher number of serious adverse events and deaths at the higher daily dose, the risk-benefit ratio for the OTC switch of the higher strength formulation appears unfavorable, even though the risks of SAE and death are low.

Currently, Australia is the only country in which 20 mg famotidine tablets are available OTC. Experience with the higher strength tablet marketed OTC is therefore limited. Many other drugs with heartburn indications are currently available OTC in the USA, including other H₂ blockers, antacids, and a proton pump inhibitor. Since the public has already several options in the OTC marketplace, this reviewer does not find a public health advantage to an OTC switch of the higher strength tablet, 20 mg famotidine formulation that would balance a possibly higher incidence of severe adverse events.

Many consumers may take the higher strength tablet automatically, thinking that it is better, although the higher dose may not be needed.

B. Recommendations

This reviewer does not recommend approval of the present application. The safety data from clinical trials submitted in this application establish only that the frequency of common side effects (such as headache, constipation, diarrhea, and dizziness) is similar for famotidine 20 mg and famotidine 10 mg. However, available post-marketing surveillance and marketing data indicate increased numbers of serious adverse events and deaths at the higher 40 mg daily dose when compared to the 20 mg daily dose that is currently available OTC. Although the risks of serious events are low, the available information does not establish a favorable risk-benefit ratio for OTC approval of the higher strength formulation, since the medication provides only symptomatic relief for a condition which is not life-threatening and for which other treatment options are available.

Available information from the literature supports the current prescription famotidine labeling information that recommends dosage reduction by one half for patients with moderate or severe renal insufficiency (defined as creatinine clearance <50 mL/min). If the higher strength oral famotidine formulation is approved OTC, some means would be required to implement a dose reduction in patients with impaired renal function.

However, in an OTC setting, creatinine clearance values will not be available to consumers who self-medicate. Moreover, in elderly patients the creatinine clearance can be greatly overestimated from BUN and creatinine values, because of decreased muscle mass. Many elderly people have silent renal insufficiency and may not be aware, or have never been told by their doctors, that they have reduced renal function. An alternative method is needed to guide OTC consumers, using a surrogate marker that is easily understood, generally available, and reasonably well correlated with creatinine clearance. For famotidine, age is the obvious marker.

This direction would protect many OTC famotidine users, because the median age of these consumers is estimated as 50 from the actual use trial submitted for this application, and because the serious adverse events involving famotidine occur more frequently in older patients .

Reviews of postmarketing reports and the clinical literature revealed the rare occurrence of the following unlisted events, for which the relationship to therapy may be unclear: aplastic anemia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, QT prolongation, rhabdomyolysis, hepatic necrosis, hepatic failure, hepatitis, mixed hepatocellular jaundice, pancreatitis, and carcinoid tumor. This information will be shared with HFD-180 for further consideration.

XI. Appendix

A. Adverse Events by Body Systems in Prevention Clinical Trials

Number (%) of Patients With Specific Clinical Adverse Experiences by Body System
Double-Blind Phase (N=794)

	Famotidine 20 mg		Famotidine 10 mg		Placebo	
	n (%)	DR	n (%)	DR	n (%)	DR
Total patients	261		271		262	
Patients with no adverse experience (AE)	252 (96.6)		261 (96.3)		252 (96.2)	
Patients with one or more AEs	9 (3.4)	1	10 (3.7)	2	10 (3.8)	2
Body as a Whole	1 (0.4)	1	2 (0.7)	0	1 (0.4)	1
Asthenia/fatigue	0 (0.0)		1 (0.4)	0	0 (0.0)	
Pain, abdominal	1 (0.4)	1	1 (0.4)	0	1 (0.4)	1
Digestive System	2 (0.8)	0	2 (0.7)	1	3 (1.1)	0
Diarrhea	1 (0.4)	0	0 (0.0)		0 (0.0)	
Dyspepsia	0 (0.0)		0 (0.0)		1 (0.4)	0
Nausea	0 (0.0)		2 (0.7)	1	1 (0.4)	0
Vomiting	1 (0.4)	0	1 (0.4)	1	1 (0.4)	0
Musculoskeletal Disorders	1 (0.4)	0	0 (0.0)		1 (0.4)	0
Arthritis	0 (0.0)		0 (0.0)		1 (0.4)	0
Pain, back	1 (0.4)	0	0 (0.0)		0 (0.0)	
Nervous System and Psychiatric	5 (1.9)	0	4 (1.5)	0	4 (1.5)	1
Headache	5 (1.9)	0	4 (1.5)	0	4 (1.5)	1
Respiratory System Disorders	0 (0.0)		3 (1.1)	1	1 (0.4)	0
Congestion, nasal	0 (0.0)		1 (0.4)	1	0 (0.0)	
Dyspnea	0 (0.0)		1 (0.4)	0	0 (0.0)	
Infection, respiratory, upper	0 (0.0)		1 (0.4)	0	0 (0.0)	
Sinusitis	0 (0.0)		0 (0.0)		1 (0.4)	0
No significant differences between treatment groups were observed.						
DR = Drug-related. Numbers in this column refer to patients with adverse experiences considered by the investigator to be possibly related to study drug (none were probably or definitely related).						
Although a patient may have had two or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.						

P114 Listing of As by Body System

Number (%) of Patients With Specific Clinical Adverse Experiences by Body System
 Double-Blind Phase
 All-Patients-Treated (N=1229)

	Famotidine 20 mg		Famotidine 10 mg		Placebo	
	n (%)	DR	n (%)	DR	n (%)	DR
Total patients	489		491		249	
Patients with no adverse experience (AE)	477(97.5)		475(96.7)		238(96.2)	
Patients with one or more AEs	12 (2.5)	3	16 (3.3)	6	11 (4.4)	5
Body as a Whole	1 (0.2)	0	2 (0.4)	0	2 (0.8)	1
Edema/swelling	0 (0.0)		0 (0.0)		1 (0.4)	0
Pain, abdominal	1 (0.2)	0	1 (0.2)	0	1 (0.4)	1
Pain, chest	0 (0.0)		1 (0.2)	0	0 (0.0)	
Digestive System	3 (0.6)	2	4 (0.8)	1	1 (0.4)	0
Diarrhea	1 (0.2)	1	2 (0.4)	1	0 (0.0)	
Nausea	2 (0.4)	1	1 (0.2)	0	1 (0.4)	0
Vomiting	0 (0.0)		1 (0.2)	0	0 (0.0)	
Nervous System and Psychiatric	8 (1.6)	2	9 (1.8)	5	9 (3.6)	4
Dizziness	1 (0.2)	0	1 (0.2)	0	1 (0.4)	0
Headache	7 (1.4)	2	7 (1.4)	4	8 (3.2)	4
Migraine	0 (0.0)		1 (0.2)	1	0 (0.0)	
Respiratory System Disorders	1 (0.2)	0	1 (0.2)	0	0 (0.0)	
Pharyngitis	0 (0.0)		1 (0.2)	0	0 (0.0)	
Sneezing	1 (0.2)	0	0 (0.0)		0 (0.0)	
Special Sense Disorders	0 (0.0)		1 (0.2)	0	0 (0.0)	
Tinnitus	0 (0.0)		1 (0.2)	0	0 (0.0)	

No significant differences between treatment groups were observed.

DR = Drug related. Numbers in this column refer to patients with adverse experiences considered by the investigator to be possibly or probably related to study drug (none were definitely related).

Although a patient may have had two or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

P117 Listing of As by Body System

Number (%) of Patients With Specific Clinical Adverse Experiences by Body System
 Double-Blind Phase
 All-Patients-Treated (N=1334)

	Famotidine 20 mg			Famotidine 10 mg			Placebo		
	n	(%)	DR	n	(%)	DR	n	(%)	DR
Total patients	532			537			265		
Patients with one or more AEs	4	(0.8)	1	5	(0.9)	1	2	(0.8)	0
Patients with no adverse experience (AE)	528	(99.2)		532	(99.1)		263	(99.2)	
Digestive System	2	(0.4)	1	3	(0.6)	1	2	(0.8)	0
Nausea	1	(0.2)	1	2	(0.4)	1	2	(0.8)	0
Vomiting	2	(0.4)	1	3	(0.6)	0	1	(0.4)	0
Nervous System and Psychiatric	3	(0.6)	0	1	(0.2)	1	0	(0.0)	
Headache	3	(0.6)	0	1	(0.2)	1	0	(0.0)	
Respiratory System Disorders	0	(0.0)		1	(0.2)	0	0	(0.0)	
Asthma	0	(0.0)		1	(0.2)	0	0	(0.0)	
Skin and Skin Appendage Disorders	0	(0.0)		1	(0.2)	0	0	(0.0)	
Flushing	0	(0.0)		1	(0.2)	0	0	(0.0)	
No significant differences between treatment groups were observed. DR = Drug related. Numbers in this column refer to patients with adverse experiences considered by the investigator to be possibly related to study drug (none were probably or definitely related). Although a patient may have had two or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.									

P128 Listing of As by Body System

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ON ORIGINAL**

Number (%) of Patients With Specific Clinical Adverse Experiences by Body System—
Double-Blind Phase—
All Randomized Patients (N=287)

	Famotidine 20 mg		Placebo	
	n (%)	DR	n (%)	DR
Total patients	143		144	
Patients with no adverse experience (AE)	134 (93.7)		131 (91.0)	
Patients with one or more AEs	9 (6.3)	2	13 (9.0)	5
Body as a Whole	1 (0.7)	1	0 (0.0)	
Pain, abdominal	1 (0.7)	1	0 (0.0)	
Digestive System	1 (0.7)	1	5 (3.5)	3
Diarrhea	0 (0.0)		2 (1.4)	1
Nausea	0 (0.0)		2 (1.4)	2
Vomiting	1 (0.7)	1	1 (0.7)	0
Musculoskeletal Disorders	1 (0.7)	0	1 (0.7)	0
Pain, foot	0 (0.0)		1 (0.7)	0
Pain, neck	1 (0.7)	0	0 (0.0)	
Nervous System and Psychiatric	2 (1.4)	0	4 (2.8)	1
Dizziness	0 (0.0)		1 (0.7)	1
Headache	2 (1.4)	0	3 (2.1)	1
Seizure, grand mal	0 (0.0)		1 (0.7)	0
Respiratory System Disorders	3 (2.1)	0	2 (1.4)	0
Infection, respiratory	1 (0.7)	0	0 (0.0)	
Infection, respiratory, upper	2 (1.4)	0	2 (1.4)	0
Special Sense Disorders	1 (0.7)	0	1 (0.7)	1
Eustachian tube disorder	1 (0.7)	0	0 (0.0)	
Perversion, taste	0 (0.0)		1 (0.7)	1
DR = Drug related. Numbers in this column refer to patients with adverse experiences considered by the investigator to be possibly or probably related to study drug (none were definitely related).				
Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.				

P137 AE listing by body system.

Number (%) of Patients With Specific Clinical Adverse Experiences
by Body System (N=523)

	Famotidine 20 mg	
	N (%)	DR
Total patients	523	
Patients with one or more adverse experiences	46 (8.8)	31
Patients with no adverse experience	477 (91.2)	
Body as a Whole	12 (2.3)	9
Asthenia/fatigue	2 (0.4)	2
Distention, abdominal	2 (0.4)	1
Pain, abdominal	7 (1.3)	5
Pain, chest	1 (0.2)	1
Cardiovascular System	2 (0.4)	0
Blood pressure increased	1 (0.2)	0
Phlebitis/thrombophlebitis	1 (0.2)	0
Digestive System	27 (5.2)	20
Constipation	11 (2.1)	11
Diarrhea	9 (1.7)	6
Dry mouth	2 (0.4)	2
Dyskinesia, esophageal	1 (0.2)	0
Flatulence	3 (0.6)	2
Nausea	3 (0.6)	1
Stomatitis, aphthous	1 (0.2)	0
Musculoskeletal Disorders	2 (0.4)	1
Fracture, knee	1 (0.2)	0
Heaviness, regional	1 (0.2)	1
Nervous System and Psychiatric Disorders	11 (2.1)	8
Dizziness	3 (0.6)	2
Entrapment, nerve	1 (0.2)	0
Euphoria	1 (0.2)	1
Headache	6 (1.1)	5
Somnolence	1 (0.2)	1

P119 Listing of As by Body System

B. Most Common Adverse Events by Body System for Post-Marketing Reports

Most Common[†] Adverse Experiences for Famotidine 10 mg (In Order of Most Common System Organ Class [SOC])—
Spontaneous WAES Reports From Healthcare Professionals

Adverse Experience Term	Number of Reports
Gastrointestinal Disorders	409
Constipation	117
Dry mouth	107
Diarrhoea NOS	98
Loose stools	39
Nausea	20
Abdominal pain, NOS	17
General Disorders and Administration Site Conditions	241
Malaise	149
Thirst	26
Pyrexia	25
Drug ineffective	16
Asthenia	15
Chest pain	14
Skin and Subcutaneous Tissue Disorders	155
Pruritus NOS	54
Rash NOS	46
Pallor	25
Urticaria NOS	22
Cold sweat	21
Face oedema	6
Respiratory, Thoracic, and Mediastinal Disorders	89
Respiratory distress	36
Pharyngolaryngeal pain	33
Dyspnoea NOS	14
Laryngeal pain	5
Dry Throat	2
Oropharyngeal swelling	2
Throat tightness	2
Nervous System Disorders	84
Headache NOS	25
Dizziness	16
Somnolence	14
Hypoaesthesia	13
Syncope	3
Tremor	3
<p>[†] The 6 most common AERs for the most frequent SOCs. There may be more than 6 if there are multiple AERs that have the same number of events as the AER that makes the 6th most common. Reports with more than one adverse experience are counted in the body system pertaining to each adverse experience. Therefore, the sum of adverse experiences may be larger than the total number of reports.</p> <p>WAES = Worldwide adverse experience system. AER = Adverse experience report. NOS = Not otherwise specified.</p>	

Most Common[†] Adverse Experiences for Famotidine 20 mg (In Order of Most Common System Organ Class [SOC])—
Spontaneous WAES Reports From Healthcare Professionals

Adverse Experience Term	Number of Reports
General Disorders and Administration Site Conditions	128
General symptom NOS	31
Drug ineffective	19
Pyrexia	16
Asthenia	13
Drug interaction NOS	12
Oedema NOS	11
Skin and Subcutaneous Tissue Disorders	104
Rash NOS	29
Pruritus NOS	20
Alopecia	13
Angioneurotic oedema	7
Face oedema	7
Hypotrichosis	6
Urticaria NOS	6
Gastrointestinal Disorders	101
Nausea	22
Diarrhoea NOS	20
Vomiting NOS	10
Abdominal pain NOS	9
Abdominal pain upper	9
Dyspepsia	8
Blood and Lymphatic System Disorders	98
Thrombocytopenia	32
Pancytopenia	16
Leukopenia NOS	13
Neutropenia	12
Agranulocytosis	7
Anaemia NOS	7
Nervous System Disorders	97
Headache NOS	23
Dizziness	19
Paraesthesia	10
Dysgeusia	7
Grand mal convulsion	5
Burning sensation	4
Convulsions NOS	4
Depressed level consciousness	4
Syncope	4
Psychiatric Disorders	65
Confusion	18
Mental disorder NOS	16
Hallucinations NOS	12
Depression	9
Disorientation	9
Anxiety NEC	8
<p>[†] The 6 most common AERs for the most frequent SOCs. There may be more than 6 if there are multiple AERs that have the same number of events as the AER that makes the 6th most common. Reports with more than one adverse experience are counted in the body system pertaining to each adverse experience. Therefore, the sum of adverse experiences may be larger than the total number of reports.</p> <p>WAES = Worldwide adverse experience system. AER = Adverse experience report. NOS = Not otherwise specified. NEC = Not elsewhere classified.</p>	

Most Common[†] Adverse Experiences for Famotidine 40 mg (In Order of Most Common System Organ Class [SOC])—
Spontaneous WAES Reports From Healthcare Professionals

Adverse Experience Term	Number of Reports
General Disorders and Administration Site Conditions	151
General symptoms NOS	53
Drug ineffective	27
Drug interaction NOS	20
Pyrexia	13
Asthenia	10
Malaise	9
Skin and Subcutaneous Tissue Disorders	120
Rash NOS	26
Alopecia	16
Urticaria NOS	15
Pruritus NOS	11
Angioneurotic oedema	8
Photosensitivity reaction NOS	6
Stevens Johnson syndrome	6
Toxic epidermal necrolysis	6
Nervous System Disorders	95
Headache NOS	20
Dizziness	13
Paraesthesia	10
Convulsions NOS	7
Dysgeusia	7
Somnolence	5
Gastrointestinal Disorders	92
Abdominal pain NOS	17
Diarrhoea NOS	17
Nausea	17
Vomiting NOS	7
Dry mouth	4
Dyspepsia	4
Pancreatitis NOS	4
Blood and Lymphatic System Disorders	77
Thrombocytopenia	25
Leukopenia NOS	12
Pancytopenia	12
Agranulocytosis	10
Anaemia NOS	7
Bone marrow depression	5
Neutropenia	5
Psychiatric Disorders	74
Mental disorder NOS	29
Hallucinations NOS	19
Confusion	16
Psychotic disorder NOS	14
Agitation	7
Depression	7
Insomnia	7
[†] The 6 most common AERs for the most frequent SOCs. There may be more than 6 if there are multiple AERs that have the same number of events as the AER that makes the 6 th most common. Reports with more than one adverse experience are counted in the body system pertaining to each adverse experience. Therefore, the sum of adverse experiences may be larger than the total number of reports. WAES = Worldwide adverse experience system. AER = Adverse experience report. NOS = Not otherwise specified.	

Most Common[†] Adverse Experiences for Famotidine, Miscellaneous/Other Dosages (In
Order of Most Common System Organ Class [SOC])—
Spontaneous WAES Reports From Healthcare Professionals

Adverse Experience Term	Number of Reports
General Disorders and Administration Site Conditions	280
General symptom NOS	67
Pyrexia	47
Drug interaction NOS	33
Drug ineffective	32
Asthemia	23
Malaise	17
Blood and Lymphatic System Disorders	259
Thrombocytopenia	119
Leukopenia NOS	37
Agranulocytosis	30
Neutropenia	23
Pancytopenia	23
Anaemia NOS	15
Skin and Subcutaneous Tissue Disorders	254
Rash NOS	82
Pruritus NOS	41
Alopecia	27
Urticaria NOS	17
Face oedema	12
Hypotrichosis	12
Gastrointestinal Disorders	240
Nausea	45
Diarrhoea NOS	34
Vomiting NOS	34
Dyspepsia	18
Abdominal pain NOS	17
Constipation	14
Nervous System Disorders	221
Headache NOS	47
Dizziness	34
Dysgeusia	27
Tremor	16
Convulsions NOS	13
Hypoesthesia	9
Neurological disorder NOS	9
Paraesthesia	9
Somnolence	9
Psychiatric Disorders	187
Confusion	60
Mental disorder NOS	44
Hallucinations NOS	32
Depression	27
Insomnia	24
Agitation	21
<p>[†] The 6 most common AERs for the most frequent SOCs. There may be more than 6 if there are multiple AERs that have the same number of events as the AER that makes the 6th most common. Reports with more than one adverse experience are counted in the body system pertaining to each adverse experience. Therefore, the sum of adverse experiences may be larger than the total number of reports. WAES = Worldwide adverse experience system. AER = Adverse experience report. NOS = Not otherwise specified.</p>	

C. Listing of WAES report numbers

Table 32. WAES reports of SAEs, at least one event evaluated as possible or probable

WAES 00011097	WAES 01061067	WAES 87050352	WAES 94015519	WAES 98011267
WAES 00011506	WAES 01061207	WAES 87060452	WAES 94030653	WAES 98011268
WAES 00011514	WAES 01061487	WAES 87060466	WAES 94040172	WAES 98012543
WAES 00011789	WAES 01061493	WAES 87070363	WAES 94040231	WAES 98012544
WAES 00020517	WAES 01062551	WAES 87080006	WAES 94040281	WAES 98012545
WAES 00020765	WAES 01062667	WAES 87080271	WAES 94040544	WAES 98021542
WAES 00021130	WAES 01070544	WAES 87090002	WAES 94050399	WAES 98021544
WAES 00021881	WAES 01070688	WAES 87100480	WAES 94050401	WAES 98022067
WAES 00031475	WAES 01070690	WAES 87110081	WAES 94051343	WAES 98030081
WAES 00031572	WAES 01071086	WAES 87110213	WAES 94060865	WAES 98030907
WAES 00035713	WAES 01071138	WAES 87110481	WAES 94061020	WAES 98036185
WAES 00042355	WAES 01071407	WAES 87120009	WAES 94065501	WAES 98040884
WAES 00042560	WAES 01072799	WAES 88020755	WAES 94077718	WAES 98041570
WAES 00050262	WAES 01080306	WAES 88040181	WAES 94077730	WAES 98041579
WAES 00051179	WAES 01080620	WAES 88050012	WAES 94090268	WAES 98041580
WAES 00052047	WAES 01080920	WAES 88050195	WAES 94090329	WAES 98050733
WAES 00052503	WAES 01081159	WAES 88050390	WAES 94090350	WAES 98051653
WAES 00052633	WAES 01082912	WAES 88060743	WAES 94105522	WAES 98051654
WAES 00060389	WAES 01083235	WAES 88080392	WAES 94110668	WAES 98051869
WAES 00060734	WAES 01086045	WAES 88090164	WAES 94110736	WAES 98061786
WAES 00061180	WAES 01090113	WAES 88090167	WAES 95010078	WAES 98061788
WAES 00062323	WAES 01090349	WAES 88090340	WAES 95010616	WAES 98061791
WAES 00062369	WAES 01090682	WAES 88090532	WAES 95011067	WAES 98070060
WAES 00062415	WAES 01091036	WAES 88120190	WAES 95020858	WAES 98070061
WAES 00062525	WAES 01091454	WAES 88120630	WAES 95021061	WAES 98070063
WAES 00062643	WAES 01091618	WAES 89010297	WAES 95035512	WAES 98070226
WAES 00063027	WAES 01092046	WAES 89010729	WAES 95035550	WAES 98070814
WAES 00063252	WAES 01092269	WAES 89020156	WAES 95040832	WAES 98070815
WAES 00064584	WAES 01100646	WAES 89030852	WAES 95045019	WAES 98071504
WAES 00064585	WAES 01101477	WAES 89050461	WAES 95050711	WAES 98071505
WAES 00064586	WAES 01101876	WAES 89050548	WAES 95051049	WAES 98080271
WAES 00071573	WAES 01102435	WAES 89070546	WAES 95056024	WAES 99126021
WAES 00072328	WAES 01102996	WAES 89080641	WAES 95056068	WAES 98090492
WAES 00072411	WAES 01104451	WAES 89090148	WAES 95056081	WAES 98090495
WAES 00072514	WAES 01104774	WAES 89090389	WAES 95059112	WAES 98091550
WAES 00072515	WAES 01110740	WAES 89090667	WAES 95067702	WAES 98100036
WAES 00079119	WAES 01111038	WAES 89100427	WAES 95071674	WAES 98100039
WAES 00080655	WAES 01111974	WAES 89110047	WAES 95110987	WAES 98101465
WAES 00081202	WAES 01112108	WAES 90010777	WAES 95111243	WAES 98101466
WAES 00082263	WAES 01112311	WAES 90020229	WAES 95111539	WAES 98110541
WAES 00082327	WAES 01112410	WAES 90031175	WAES 95120670	WAES 98111342
WAES 00082462	WAES 01112446	WAES 90040324	WAES 95121398	WAES 98111891
WAES 00083120	WAES 01114697	WAES 90051207	WAES 96011196	WAES 98121280
WAES 00090178	WAES 01114698	WAES 90060235	WAES 96015549	WAES 98126067
WAES 00091627	WAES 0112USA01145	WAES 90060292	WAES 96020195	WAES 99010315
WAES 00091801	WAES 0112USA01718	WAES 90060713	WAES 96025071	WAES 99010531
WAES 00092036	WAES 0112USA01720	WAES 90070190	WAES 96025502	WAES 99011111

WAES 00092534	WAES 0112USA02368	WAES 90070567	WAES 96031042	WAES 99011392
WAES 00100913	WAES 0112USA02529	WAES 90091003	WAES 96031226	WAES 99011682
WAES 00101151	WAES 0112USA02531	WAES 90100438	WAES 96032032	WAES 99020169
WAES 00101152	WAES 0112USA02567	WAES 90100684	WAES 96051034	WAES 99020285
WAES 00101153	WAES 0201USA00284	WAES 90120807	WAES 96051592	WAES 99020286
WAES 00101423	WAES 0201USA00870	WAES 91010525	WAES 96052151	WAES 99020753
WAES 00101547	WAES 0201USA01727	WAES 91011344	WAES 96060607	WAES 99021655
WAES 00101548	WAES 0201USA03350	WAES 91020084	WAES 96061007	WAES 99025596
WAES 00101549	WAES 0201USA03367	WAES 91030235	WAES 96061008	WAES 99030226
WAES 00102276	WAES 0202USA01824	WAES 91031554	WAES 96061345	WAES 99030227
WAES 00102601	WAES 0202USA01966	WAES 91040501	WAES 96062012	WAES 99041000
WAES 00106087	WAES 0203USA00338	WAES 91040761	WAES 96062216	WAES 99041001
WAES 00110311	WAES 0203USA00405	WAES 91060862	WAES 96082417	WAES 99041002
WAES 00110941	WAES 0203USA01118	WAES 91080734	WAES 96082491	WAES 99041003
WAES 00111382	WAES 0203USA01288	WAES 91091351	WAES 96091633	WAES 99041258
WAES 00111929	WAES 0203USA01311	WAES 91110159	WAES 96092317	WAES 99041487
WAES 00111930	WAES 0203USA02553	WAES 91110804	WAES 96102199	WAES 99041589
WAES 00120163	WAES 0203USA03025	WAES 91120165	WAES 96109752	WAES 99041631
WAES 99122126	WAES 0203USA03188	WAES 91120231	WAES 96111868	WAES 99050386
WAES 00120539	WAES 0203USA03331	WAES 92040451	WAES 96116144	WAES 99050666
WAES 00120555	WAES 0204USA01025	WAES 92045540	WAES 96120314	WAES 99051233
WAES 00122126	WAES 0204USA01458	WAES 92090513	WAES 96120346	WAES 99051681
WAES 00122242	WAES 0204USA02655	WAES 92095544	WAES 96120656	WAES 99060061
WAES 01011037	WAES 0205USA00212	WAES 92095548	WAES 96121727	WAES 99060240
WAES 01012379	WAES 0205USA00336	WAES 92095550	WAES 96126147	WAES 99061017
WAES 01019110	WAES 0205USA01486	WAES 92095551	WAES 97011233	WAES 99061096
WAES 01020438	WAES 0205USA01773	WAES 92127270	WAES 97012408	WAES 99066013
WAES 01020683	WAES 0205USA02278	WAES 93020031	WAES 97020659	WAES 99071056
WAES 01021013	WAES 0205USA02661	WAES 93025513	WAES 97021794	WAES 99071997
WAES 01021510	WAES 0205USA02663	WAES 93030042	WAES 97036102	WAES 99090310
WAES 01025022	WAES 0205USA03218	WAES 93047703	WAES 97051378	WAES 99090312
WAES 01030453	WAES 0205USA03352	WAES 93050990	WAES 99122289	WAES 99090875
WAES 01030935	WAES 0206USA00186	WAES 93060510	WAES 97061581	WAES 99090955
WAES 01031633	WAES 0206USA00930	WAES 93060841	WAES 97061864	WAES 99091251
WAES 01031686	WAES 0206USA01086	WAES 93061293	WAES 97065083	WAES 99100858
WAES 01032977	WAES 0206USA01655	WAES 93071004	WAES 97070818	WAES 99101230
WAES 01033123	WAES 0206USA01656	WAES 93071300	WAES 97071592	WAES 99101232
WAES 01033243	WAES 0206USA01800	WAES 93080500	WAES 97080036	WAES 99111563
WAES 01033554	WAES 0212USA00620	WAES 93085530	WAES 97080379	WAES 99120048
WAES 01040154	WAES 0303USA01690	WAES 93086016	WAES 97081767	WAES 99120613
WAES 01040492	WAES 0304USA01607	WAES 93090237	WAES 97081875	WAES 99120726
WAES 01041236	WAES 86040732	WAES 93101285	WAES 97085555	WAES 99120859
WAES 01041391	WAES 86040737	WAES 93110378	WAES 97091356	WAES 99120864
WAES 01041430	WAES 86090009	WAES 93120007	WAES 97100624	WAES 99120957
WAES 01041618	WAES 87010097	WAES 93120172	WAES 97102101	WAES 99122071
WAES 01041657	WAES 87020168	WAES 93121150	WAES 97111359	
WAES 01041692	WAES 87020312	WAES 94010318	WAES 97111360	
WAES 01041721	WAES 87020604	WAES 94010320	WAES 97120357	
WAES 01042767	WAES 87030564	WAES 94010322	WAES 97120669	
WAES 01052347	WAES 87040017	WAES 94010323	WAES 97121097	
WAES 01060055	WAES 87040051	WAES 94010426	WAES 97121100	

WAES 01060157	WAES 87040421	WAES 94010585	WAES 98011007	
WAES 01060816	WAES 87040622	WAES 94011027	WAES 98011266	

D. Narratives and Comments, WAES reports of Deaths

Causality was in most cases evaluated as 'possible' for at least one AE term, not necessarily the death event itself. Confounding factors, such as concomitant medications, and the underlying medical condition of the subjects, were often present. If a contribution of famotidine was possible, despite confounding factors, the event was evaluated as possible. If the contribution of famotidine was significantly more likely than any other factor, the event was rated 'probable'. For the definitions of 'highly probable', 'unlikely', and 'not related' evaluations, see Table 28. Where units are missing for laboratory values, they were not provided in the case narratives. The case narratives were taken from the Sponsor's submission with only minor edits.

WAES 0204USA01458 (Japan) PANCYTOPENIA, RENAL FAILURE ACUTE; CONVULSIONS NOS (not otherwise specified) A 77 year old hospitalized male with severe pneumonia nos and chronic renal failure on 09-MAR-2002 was placed on therapy with famotidine, tablet, 20 mg, once a day for the treatment of a bleeding gastric ulcer. Other concomitant therapy included allopurinol, furosemide, enalapril maleate, minocycline HCl, cefazopran HCl, and cilastatin sodium (+) imipenem. On _____, prior to therapy with famotidine the patient's lab values were: blood hemoglobin test 6.6 g/dl, blood platelet count $17.8 \times 10^4/\text{mm}^3$, white blood cell count $13400/\text{mm}^3$, whole blood hematocrit 21.0%, serum blood urea nitrogen (BUN) 75.0 mg/dL, and serum creatinine 3.47 mg/dL. On 18-MAR-2002 the patient developed pancytopenia and therapy with famotidine was discontinued. On _____ the patient's lab values were: blood hemoglobin test 4.9 g/dL, blood platelet count $20.5 \times 10^4/\text{mm}^3$, serum blood urea nitrogen test 19.1 mg/d, white blood cell count $5100/\text{mm}^3$, whole blood hematocrit 15.4 %, serum creatinine test 2.59 mg/dL. On 23-MAR-2002 the patient recovered from the pancytopenia. On _____ the patient's lab values were: blood hemoglobin test 5.3 g/dL, whole blood hematocrit 16.7%, white blood cell count $15300/\text{mm}^3$, serum creatinine test 2.77 mg/dL, serum blood urea nitrogen test 32.2 mg/dL, blood platelet count 22.2×10^4 . On 26-MAR-2002 the patient was started on therapy with famotidine (injection), 20 mg IV twice daily. On _____ the patient's lab values were: blood hemoglobin test 10.4 g/dL, blood platelet count $11.8 \times 10^4/\text{mm}^3$, whole blood hematocrit 30.9%, white blood cell count $14100/\text{mm}^3$, serum creatinine test 2.77 mg/dL. On 01-APR-2002 the patient was restarted on therapy with famotidine 20 mg tablet twice daily. _____ the patient's lab values were: blood hemoglobin test 12.2 g/dL, whole blood hematocrit 36.9 %, white blood cell count $10700/\text{mm}^3$, serum creatinine test 2.22 mg/dL, serum blood urea nitrogen test 67.5 mg/dL, and blood platelet count $6.7 \times 10^4/\text{mm}^3$. On _____ the patient's lab values were: blood hemoglobin test 9.8 g/dL, serum blood urea nitrogen test 42.3 mg/dL, whole blood hematocrit 30.5%, white blood cell count $10800/\text{mm}^3$, serum creatinine test 2.05 mg/dL, and blood platelet count $5.6 \times 10^4/\text{mm}^3$. On 08-APR-2002 therapy with famotidine tablets was discontinued. On _____ the patient's lab values were: blood hemoglobin test 8.1 g/dL, whole blood hematocrit 24.9 %, white blood cell count $11400/\text{mm}^3$, blood platelet count $10.8 \times 10^4/\text{mm}^3$, BUN 86.9 mg/dL and serum creatinine 2.35 mg/dL. On _____ the patient had an onset of convulsion and died.

Comment: The patient's heme parameters are related to dechallenge and rechallenge with famotidine although it appears that there may have been a blood transfusion sometime between

WAES 89020156-(Japan) -- BONE MARROW DEPRESSION NOS; APLASTIC ANAEMIA; GENERAL SYMPTOM NOS; HAEMODIALYSIS PULMONARY OEDEMA NOS; RENAL FAILURE NOS; RESPIRATORY FAILURE (EXCL NEONATAL); THROMBOCYTOPENIA; VASCULITIS NOS. A 76-year-old hospitalized female with a history of renal failure, hemodialysis, pulmonary edema, thrombocytopenia, vasculitis, and anemia entered a postmarketing surveillance study abroad conducted by Yamanouchi Pharmaceutical Co., Ltd. She was placed on therapy with Pepcid 10 mg daily, on 06FEB87 to treat endoscopically seen multiple, acute gastric ulcers with blood clots. Concomitant medication included prednisolone, haloperidol and biperiden. On 11FEB87 bleeding spots appeared in the lower thigh. A bone marrow examination revealed hypoplasia and aplastic changes in all cell types. Laboratory evaluation on _____ revealed hemoglobin 5.3, hematocrit 16.4, platelet count 3, WBC 3800. BUN 53 and creatinine 4.4. Pretreatment tests on _____ following dialysis revealed hemoglobin 6.2, hematocrit 18.8, platelet count 9.1, WBC 7200, neutrophils 8, segmented neutrophils 70, eosinophils 0, basophils 0, monocytes 5, lymphocytes 14, alkaline phosphatase 95, LDH 302, BUN 56, and creatinine 4.7. Therapy with Pepcid was discontinued on 11FEB87. The patient subsequently died on _____ due to respiratory failure. The investigator felt that the thrombocytopenia rapidly became worse and led to pancytopenia following the initiation of therapy with Pepcid; consequently, the investigator felt that the pancytopenia was probably related to therapy with Pepcid.

Comment Although the patient had preexisting renal insufficiency, thrombocytopenia, and vasculitis, the investigator felt that the patient's thrombocytopenia rapidly worsened (9.1 to 3.0) and led to pancytopenia following initiation of therapy with famotidine. The investigator felt the pancytopenia was probably related to therapy with Pepcid. Other medications are unlikely to have contributed to this event. The haldol label states there have been reports citing mild and usually transient leukopenia, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis. Agranulocytosis has rarely been reported to have occurred, and then only in association with other medications. Little has been reported in Micromedex Drug Dex Evaluations with regard to hematologic events and biperiden. Prednisolone would raise rather than depress WBC counts.

WAES 90010777 (Belgium) HEPATIC NECROSIS. A 73-year old male with a history of a positive antibody to hepatitis B surface antigen, on 05MAY89, was placed on therapy with famotidine 40 mg, PO, daily for the treatment of a peptic ulcer. There were no concomitant medications. On _____, the patient developed jaundice. That same day, laboratory analysis revealed SGOT 1250, SGPT 2120 and total serum bilirubin 25.6. On 22JUN89, therapy with the study drug was discontinued. Subsequently, the patient was hospitalized and he died due to "fulminant hepatic failure". An autopsy revealed hepatic necrosis. The reporting physician felt that the patient's experiences were probably related to therapy with famotidine.

Comment: This case of fulminant hepatic failure and hepatic necrosis may possibly be related to therapy with famotidine. We however do not know what the patient's baseline LFT's were and he was hepatitis B surface antigen positive.

WAES 95111539(Japan) NEUTROPENIA; ANAEMIA NOS A 40-year-old female with polymyositis who in June 1995 was placed on therapy with famotidine 20 mg bid. Concomitant therapy included aluminum hydroxide gel-magnesium hydroxide (Maalox), alfacalcidol (Onealfa) and prednisolone. On [redacted] laboratory evaluation revealed WBC count of 1640 and neutrophils 311. The patient was hospitalized for examination. Because results of a bone marrow examination were normal, drug-induced or viral neutropenia was suspected. Therapy with famotidine continued. From 18SEP95 to 28SEP95, the patient was treated with G-CSF. On [redacted], laboratory evaluation revealed WBC count 4440 and neutrophils 3241, and the patient was discharged and followed on an out-patient basis. On [redacted] outpatient laboratory evaluation revealed WBC count of 1330 and neutrophils 1%, and the patient was rehospitalized. On 03OCT95, all medication, including famotidine, was discontinued. The patient's condition was treated with G-CSF, aminoglycoside IV, clindamycin IV and isoniazid (Iscotin). Therapy with prednisolone had been temporarily discontinued, but it was resumed because of increased creatine kinase levels. On [redacted] the patient died. An autopsy was not performed. The cause of death was determined to be aplastic anemia. The reporter felt that the patient's "multiple myositis" may not have been associated with the neutropenia; therefore, "a drug-induced symptom is strongly suspected."

Comments: Drug induced neutropenia is possible and the most suspect medication is famotidine. Her other medications have a very low likelihood of causing this event. It is not clear what role polymyositis played since aplastic anemia can be an autoimmune phenomenon.

WAES 96052151 (Japan) BONE MARROW DEPRESSION NOS; BACTERIAL SEPSIS; SKIN ERUPTION; HEPATIC FUNCTION ABNORMAL NOS A 72 year old female was placed on therapy with famotidine, tab, 20 mg, twice a day for the treatment of a gastric ulcer on 06FEB96. Prior therapy from 30JAN96 to 05FEB96 included famotidine(MSD), injectable, 20 mg, twice a day for the treatment of her gastric ulcer. Concomitant therapy included sucralfate. On [redacted] the patient developed generalized erythema and was hospitalized. "Mild hepatic function disorder was detected by hematological examination." On 20FEB96, all medications were discontinued since drug allergy was suspected. She was treated with iv prednisolone On [redacted] the patient developed bone marrow depression with decreased platelets (59000) and WBC count 300 (bone marrow examination was not reported). She was treated with steroid pulse therapy using methylprednisolone sodium succinate 1000 mg from 26FEB96-28FEB96 and "Gran" 150 micrograms, s.c. from 01MAR96-04MAR96. Antibiotics were administered since a fever (39-40 degrees Celsius) was recognized. There was no improvement in the patient's condition and she died on [redacted] The cause of death was sepsis.

Comment: The patient had developed erythema and some hepatic dysfunction. She apparently had a drug reaction. Bone marrow depression occurred 6 days after famotidine was discontinued. It's very unlikely that sucralfate or steroids caused bone marrow depression. This was probably due to famotidine.

WAES 96126147 HEPATIC FUNCTION ABNORMAL NOS-- A 78 year old hospitalized female patient with insulin dependent diabetes, serious infection and renal insufficiency was placed on therapy with famotidine, TAB, PO, 20 mg daily (indication unknown) on 14-JUN-96. Concomitant therapy included gentamycin, oxacillin, metronidazole, furosemide and insulin. On 19-JUN-96 the patient experienced liver function abnormalities which prolonged hospitalization. On 19-JUN-96 therapy with famotidine was discontinued. Subsequently there was improvement in liver function abnormalities. The reporting physician felt that liver function abnormalities were

related to therapy with famotidine. Later, on _____, the patient underwent surgery for perineal gangrene and death occurred during surgery. Death was not related to AEs reported with famotidine.

Comment: Famotidine probably caused the liver function abnormalities since this abnormality was not noted prior to therapy, started 5 days after therapy with AST and ALT enzyme elevation into the thousands and marked improvement occurred within a week of discontinuation of therapy. The death was apparently not related to famotidine.

WAES 98012545 A 67 year old Japanese male was hospitalized with CHF, cerebral infarction, hepatitis C, diabetes, atrial fibrillation, gastritis and a history of fever, intubation and ventricular tachycardia was placed on famotidine 10 mg bid replacing cimetidine injection for prophylaxis on _____. Concomitant therapy included Tienam (cilistatin sodium salt + imipenem), enalapril maleate, aspirin, ubiquinone 50, amiodarone hydrochloride, furosemide, glyburide, nitroglycerin, aluminum hydroxide/magnesiumhydroxide, midazolam, vecuronium bromide and potassium chloride. On 07-DEC-1997 fever of 38C developed. On _____ the patient was diagnosed with agranulocytosis with WBC of 1.0. On that same day, therapy with famotidine was discontinued. On 14-DEC-1997 pneumonia was confirmed by chest X-ray and the patient was subsequently intubated. The patient developed atrial fibrillation and on _____ the patient developed ventricular tachycardia and died despite CPR and electric shock therapy.

Comment: Although this case is confounded, several of the medications that the patient was taking could have possibly contributed to agranulocytosis including famotidine, imipenem, and vasotec.

WAES 90060713 (France) A 66 year old male was being treated for an ulcer with famotidine 20 mg po daily and was on no concomitant medications. Two months after discontinuation of famotidine treatment, the patient developed fever and was hospitalized with pancytopenia and elevated LFTs and ESR of 80. Bone marrow biopsy showed aplasia without infiltration and isolated hemogenous lymph nodules. Coombs positive hemolytic anemia was diagnosed. CMV antibody and HIV antibody testing was negative. Labs showed platelet count of 12000 and the patient continued with anemia and thrombocytopenia. The patient was hospitalized every 15 days to receive blood and platelet transfusions for over half a year. The patient developed anorexia, unspecified infections, and hematuria and developed ARDS and died. The probable cause of death was identified as hemorrhage.

Comment: The time course is so long between the time famotidine was discontinued and the development of the pancytopenia that it is unclear what caused the patient's pancytopenia and elevated LFTs. In addition, no hepatitis serologies were reported.

WAES 00064586 (Japan)--A 70 year old female developed hepatitis, respiratory insufficiency, pneumonia and encephalopathy and was hospitalized and died while on therapy with famotidine. In June 1999 the patient was started on therapy with nilvadipine and doxazosin monomethanesulfonate for the treatment of hypertension. On _____ the patient's laboratory values were as follows: total serum bilirubin (BILTOT) 0.8 MG/DL, serum aspartate aminotransferase (GOT) 21 IU/L, serum alanine aminotransferase (GPT) 21 IU/L, serum alkaline phosphatase (ALP) 199 IU/L, serum lactate dehydrogenase (LDH) 436 IU/L, and serum gamma-glutamyl transferase (GGT) 26 IU/L. However, because this regime failed to adequately control her blood pressure, her therapy with nilvadipine was switched to therapy with

losartan potassium on 02-NOV-1999. On 14-DEC-1999 the patient was placed on therapy with famotidine, tablet, 20 mg daily, for the treatment of acid reflux. Concomitant therapy included losartan potassium (MSD), tablet, 50 mg daily, for the treatment of hypertension. Other concomitant therapy included (Cardenalin), nilvadipine and rabeprazole sodium (Pariet). On _____ the patient's laboratory values were as follows: BILTOT 0.6 MG/DL, GOT 141 IU/L, GPT 180 IU/L, ALP 247 IU/L, LDH 474 IU/L, and GGT 92 IU/L. On 28-DEC-1999 the patient developed hepatic dysfunction the cause of which was unclear at the time. On _____ the patient's laboratory values were as follows: BILTOT 1.1 MG/DL, GOT 484 IU/L, GPT 587 IU/L, ALP 388 IU/L, LDH 624 IU/L, and GGT 259 IU/L. The physician recommended that the patient be admitted to the hospital for more tests and treatment but the patient refused. On _____ it was reported that a family member of the patient noticed that her skin had turned yellow so she went to the hospital. At this time a drug-induced hepatic disorder was suspected and she was admitted to the hospital. On this same day the patient's laboratory values were as follows: BILTOT 14.1 MG/DL, GOT 691 IU/L, GPT 676 IU/L, ALP 481 IU/L, LDH 659 IU/L, and GGT 272 IU/L. On 29-FEB-2000 therapy with famotidine, losartan potassium and doxazosin monomethanesulfonate was discontinued. The patient was treated with Stronger Neomynophagen C and other unspecified medications. However, her hepatic function deteriorated and on _____ she was transferred to another hospital. The patient was treated with several plasma exchanges and "steroid mini-pulse therapy". However, the patient's hepatic function did not recover. On _____ the patient's laboratory values were as follows: BILTOT 27.5 MG/DL, GOT 276 IU/L, GPT 200 IU/L, ALP 338 IU/L, LDH 549 IU/L, and GGT 57 IU/L. In approximately March 2000, the patient developed hepatic encephalopathy (Grade II), respiratory insufficiency and pneumonia. On _____ the patient's laboratory values were as follows: BILTOT 11.9 MG/DL, GOT 43 IU/L, GPT 33 IU/L, ALP 151 IU/L, LDH 621 IU/L, and GGT 28 IU/L. On _____ the patient died secondary to hepatic failure and respiratory failure as a result of a complication of pneumonia. The reporting physician stated that both famotidine and losartan potassium were suspected of "playing a role". No further information is available.

Comment: This history could be consistent with a drug induced hepatic disorder. She was taking multiple medications, famotidine among them.

WAES 00072328 A 44 year old female patient (US) developed anemia, sepsis, bradycardia, catheter site infection, disorientation, DIC, fever, headache, hemorrhage, seizure, subdural hematoma and thrombocytopenia, and was hospitalized and died while on therapy with famotidine. Patient was on famotidine, cefazolin, prostacyclin (to treat pulmonary hypertension in July 1997) and heparin. On _____ the patient developed a staphylococcus infection, was diagnosed with sepsis and hospitalized. The patient was treated with nafcillin, gentamycin and cefazolin, was discharged and subsequently experienced disorientation, fever and headache. She was rehospitalized with decreased mental status, thrombocytopenia, anemia, right heart failure. She was then treated with vancomycin, gentamycin, piperacillin sodium (+) tazocactam sodium (Zosyn), metronidazole, acetaminophen, dobutamine, furosemide, mannitol, allopurinol, midazolam and potassium. A head computed tomography scan was done which revealed a right sided holo-hemispheric subdural bleed and hematoma with a separate right temporal inraparenchymal hematoma. The following day the patient developed seizures which were controlled with intravenous phenytoin, fentanyl and lorazepam. The reporting physician reported that the hematology physicians following the patient felt that the patient's thrombocytopenia was secondary to DIC or possibly related to therapy with heparin, cefazolin or famotidine. The

patient received a platelet transfusion but did not respond. The patient died on _____ from right heart failure due to pulmonary hypertension, and sepsis, intracranial bleeding secondary to thrombocytopenia.

Comment: Agree with the hematologist's assessment.

WAES 00081202—AGRANULOCYTOSIS, PNEUMONIA--An 85 year old Japanese female with chronic renal failure, anemia, congestive heart failure, hypertension, gastritis, gastrointestinal bleeding, pleurisy, insomnia, herpes zoster, pneumonia and a history of hemorrhage with child birth and cystolithiasis developed agranulocytosis, pneumonia, and a contusion and was hospitalized and died while on therapy with famotidine. On 26-MAY-2000 the patient developed moderate gastrointestinal bleeding, and was started on therapy with lansoprazole from 26-MAY-2000 until 27-JUN-2000. On 27-JUN-2000 the patient was placed on therapy with famotidine, tablet, 10 mg daily, for the treatment of gastrointestinal bleeding. Concomitant therapy included allopurinol from 27-MAY-2000 until 26-JUL-2000. Other concomitant therapy included furosemide, amlodipine besylate, calcium carbonate, calcium polystyrene sulfonate, sorbitol, zopiclone, allopurinol, lansoprazole, and epoetin beta. On _____ the patient had hematemesis and was hospitalized. Upon admission the patient's laboratory values were hemoglobin 9.2 g/dl, hematocrit 28.5%, platelets 7800, WBC 110 (neutrophils 0%, lymphocytes 100% and others 0%). The patient was said to have preexisting pneumonia and was treated with lenograstim (Neutrogen), panipenem (+) betamipron (Carbenin), and isepamicin sulfate (Exacin), and was diagnosed with agranulocytosis. The patient continued to have hematemesis and died on _____ secondary to pneumonia.

Comment: The agranulocytosis could possibly have been related to therapy with one of her drugs although the complexity of the case does not permit clear attribution. The agranulocytosis could have contributed to the death resulting from pneumonia.

WAES 00120421--A 71 year old Japanese female with rheumatoid arthritis, uric acid increased and chronic renal failure and a history of uterine surgery developed pancytopenia and pneumonia and was hospitalized and died while on therapy with famotidine.

On 19-JAN-1997 the patient was placed on therapy with famotidine, 40 mg daily (indication not reported). Concomitant suspect therapy included allopurinol for the treatment of increased uric acid from 09-NOV-1999 until 13-NOV-2000 and methotrexate for the treatment of rheumatoid arthritis from approximately 1997 until 13-NOV-2000 (doses not reported). Other concomitant meds include linoril and cozaar. On _____ the patient presented to the hospital and was admitted. On _____ the patient's laboratory values were: white blood cell count (WBC) 400, red blood cell count (RBC) 238, and platelet count 99,000. On 13-NOV-2000 therapy with famotidine, allopurinol and methotrexate was discontinued. On _____ a chest x-ray revealed pneumonia. On _____ the patient's laboratory values were: total bilirubin 9.6, serum aspartate aminotransferase 108, and serum alanine aminotransferase 82. On 17-NOV-2000 the patient's dose of filgrastim was changed from 1 amp twice daily to 2 amps daily for the treatment of anemia. On _____ the patient's white blood cell count increased to 13700. Therapy with fluconazole was changed to miconazole. On approximately 20-NOV-2000 the patient was considered recovered from the pancytopenia. On _____ the patient's laboratory values were: RBC 330, hemoglobin 10.5 g/dL, hematocrit 30.8%, platelet count 21.9, and WBC 5760. On _____, the patient's laboratory values were: RBC 212, hemoglobin 6.8, hematocrit 20.3%, platelet count 1.3, and WBC 5100. However, on _____

— the patient died secondary to the pneumonia. The reporter felt that the pancytopenia was "most likely" related to therapy with methotrexate. The causality of pancytopenia with relationship to famotidine and allopurinol was unknown but could not be ruled out.

Comment: Agree with reporter's assessment.

WAES 00122242 APLASTIC ANAEMIA; DEHYDRATION; PNEUMONIA NOS; PHARYNGOLARYNGEAL PAIN An 84 year old Japanese female patient developed aplastic anemia, pneumonia, dehydration, and pharyngeal erythema while on therapy with famotidine. In November 22, 2000 the patient with congestive heart failure, hyperuricemia, ischemic heart disease, parkinsonism and a history of macrocytic anemia, thrombocytopenia and cerebral infarction (1990) and hospitalization was placed on therapy with famotidine, 20 mg tablet daily for the treatment of gastritis. Concomitant therapy included metildigoxin, furosemide, allopurinol, spironolactone, amantadine hydrochloride, and nitroglycerin. On _____, the patient had a fever. Patient's examination revealed a neutrophil count of 0% and the patient was admitted to the hospital with suspected secondary aplastic anemia. A bone marrow puncture test revealed myelo 0%, meta 0%, stab 0%, seg 2%, seg 3%, lymph 94%, mono 1%, eosino 0%, baso 1%, ebl 0%, at-lym 4% and elliptocytes were positive. The examination revealed pharyngeal reddening and dehydration. The patient's blood pressure was 112/60 mmHg, PO₂ was 86% and her pulse was 108 beats per minute. Blood tests revealed a white blood cell count of 600. On 04-Dec-2000 therapy with famotidine and all concomitant therapies were discontinued. The patient was treated with G-CSF (Neutrogin-lenograstim), Modacin (ceftazidime), Sulperazon (cefoperazone sodium-sulbactam sodium) and Cefamezin (cefazolin sodium). On _____ the patient's red blood cell count was 288×10^4 . Following hospitalization the patient's white blood cell count began to rise (following cessation of all therapies). The health professional reported that the patient was treated with an antibiotic and granulocyte colony stimulating factor and her white blood cell count initially rose to 20,000. However the patient's condition remained poor and she died of pneumonia.

Comment: The patient is on several therapies that could have caused the patient's hematologic problem and subsequent death.

WAES 01020683-- A 68 year old hospitalized male with hepatitis B, cirrhosis and "hyperpancreatism" developed thrombocytopenia, a worsening of cirrhosis, hepatic coma, and upper gastrointestinal hemorrhage while on therapy with famotidine.

On 23-JAN-2001 the patient was placed on therapy with famotidine, tablet, 40 mg daily, for the treatment of erosive gastritis. Secondary suspect therapy included fosfomycin calcium, for the treatment of bronchitis on 03-Jan-2001 for the duration of one day. Concomitant therapy included amino acids, furosemide, cysteine (+) glycine (+) glycyrrhizin (STRONGER NEOMINOPHAGEN C), flavin adenine dinucleotide. On _____ the patient's platelet count was 10.8. On _____ the patient developed thrombocytopenia. (platelet count 0.1) and vomited blood. On 04-FEB-2001 therapy with famotidine was discontinued. The patient was treated with "extract from hemolysed blood of young cattle, pirenzepine and platelet transfusions. On 05-FEB-2001, the patient's hematemsis was resolving but his thrombocytopenia persisted. On 09-Feb-2001 the patient was treated with prednisolone sodium succinate and on _____ the patient's platelet count increased to 97,000. The patient's treatment with prednisolone, continued. The patient developed hepatic coma (hepatic encephalopathy) due to liver cirrhosis (date not given). The patient's liver cirrhosis gradually worsened, according to the

reporter and on _____ the patient died. The cause of death was liver cirrhosis. The reporter stated that therapy with famotidine was not related to the patient's death. However, conflicting information from the reporter also stated that the possibility of famotidine involvement is considered strong.

Comment: Although this case is confounded, it is possible that drugs may possibly have contributed to the thrombocytopenia. It is not clear what may have contributed to patient's worsening liver cirrhosis. The patient had a history of hepatitis B and cirrhosis and was taking other medications. Furosemide has also had thrombocytopenia and hepatotoxicity reported with its use.

WAES 01041721 (US) A 72 year old female patient treated with famotidine, heparin, and ceftazidime experienced a decrease in blood pressure, coagulation disorder, abnormal ejection fraction, acute renal failure, renal tubular necrosis and thrombocytopenia. Meds included oral Pepcid (dose unknown) and heparin (dose unknown).

Comment: Little detail is provided for this case. Pepcid, heparin, and ceftazidime have all had thrombocytopenia occur with their use.

WAES 01080306 (Japan article) A 65 year old woman, a non-smoker, was admitted to the hospital with a 3 week history of fever that did not respond to cefixime. She had a 36 year history of sinobronchial syndrome (chronic bronchitis and chronic sinusitis) with respiratory tract infections due to haemophilus influenzae or pseudomonas aeruginosa several times a year. These infections are always accompanied by fever and purulent sputum. Auscultation of her chest detected some basal rhonchi. The transbronchial biopsy specimen from the lingual consolidation showed only nonspecific inflammation. The fever did not improve with numerous antibiotics including piperacillin, clindamycin, minocycline and imipenem, but it was resolved with naproxen, a non-steroidal anti-inflammatory drug, on the 10th hospital day. On the 15th hospital day, dyspnea, slight hemoptysis, and gross hematuria developed for the first time. A chest radiograph and CT scan showed bilateral infiltration, suggesting pulmonary hemorrhage. The CT scan also showed bleeding within the capsule of the left kidney. Respiratory failure developed, requiring mechanical ventilation. DIC developed. A suspected diagnosis of antineutrophil cytoplasmic antibody ANCA related vasculitis was made, and pulse therapy with steroids was started. After the steroid therapy, the respiratory failure and infiltration in both lungs improved. The DIC also was resolved. However, granulocytopenia, probably caused by antibiotics or famotidine, progressed from the 31st hospital day and the patient died of severe pneumonia on the 37th day.

Comment: This is a complicated case for which it is difficult to make a clear attribution. However granulocytopenia due to medications is a possibility.

WAES 01100646 (Japan)-- An 86 year old male with mild pulmonary emphysema, mild refractory tuberculosis, Sjogren's syndrome, suspected respiratory infection (from 22-AUG-2001), epigastric discomfort and a history of scrotal surgery was placed on therapy with famotidine 20 mg orally once a day for the treatment of gastritis after a check-up for anorexia on 27-AUG-2001. The previous serum platelet count on _____ was 251,000/mm³. Concomitant therapy included levofloxacin, 300 mg daily started on 22-AUG-2001 for the treatment of infection. Other concomitant therapy included lactobacillus, antibiotic resistant (as drug) (BIOFERMIN R), carbocysteine, metoclopramide hydrochloride (started on the same day as famotidine and theophylline). On _____ the patient developed thrombocytopenia with

a blood platelet count of 1.0 (10,000) and was hospitalized. On 05-SEP-2001 all therapies were discontinued. The patient was treated with platelet infusions, and massive steroid and immunoglobulin therapies were initiated. On 08-SEP-2001 the patient developed paralysis in the upper and lower left limbs. A cerebral computed tomography scan did not reveal hemorrhage or clear infarction. CNS symptoms due to vasculitis were suspected at the time of this report. The patient's thrombocytopenia, vasculitis and SLE-like dysemya persisted as of 27-SEP-2001 and the patient was still hospitalized. The reporter felt that thrombocytopenia was related to therapy with famotidine and levofloxacin and commented " it was unknown if P-ANCA positive vasculitis was pre-existing or caused by the drugs". As of _____ the patient had not recovered and was hospitalized. "Afterwards he died of bacterial pneumonitis on _____". The patient's autopsy on _____ revealed: focal glomerulonephritis, aspiration pneumonitis, auxiliary lesions including hyperplastic bone marrow, agonal pancreatitis, active chronic gastritis with remarkable lymphocytic infiltrate, persistent hepatitis with mild fibrosis, HCV positive, candidal cystitis, concentric cardiomegaly and aortic atherosclerosis with a clinical, diagnosis of SLE, ITP, and pneumonitis. The reporting physician stated that there were no causal relationships between the patient's death and famotidine and levofloxacin.

Comment: This case is confounded by the patient's medical conditions. It is possible that drugs may have contributed to the thrombocytopenia; however this would not have caused the patient's death which was attributed to bacterial pneumonia. The paralysis was attributed to the patient's vasculitis.

WAES 0112USA02368 (Japan) A 76 year old male with a cerebral infarction was placed on therapy with oral famotidine once a day (dose, duration and indication not reported) in May 1999. Concomitant therapy included aspirin, carbocysteine, diclofenac na and cefcapene pivoxil hydrochloride. On 01-AUG-2000 the patient developed Stevens-Johnson syndrome. Therapy with famotidine was discontinued. On _____ the patient died from Stevens-Johnson syndrome. Patient also had pulmonary abscesses due to methicillin resistant staph aureus.

Comment: Stevens Johnson syndrome could have been related to famotidine or other drugs that he was on.

WAES 0202USA01966 (Israel) MARCUS, ESTER-LEE ET AL; AGRANULOCYTOSIS ASSOCIATED WITH INITIATION OF FAMOTIDINE THERAPY. ANNALS OF PHARMACOTHERAPY 2002; 36: p.267-71. An 87-year-old white man was hospitalized because of fever and agranulocytosis (granulocyte count 0). Eight days prior to admission, famotidine therapy had been initiated. Famotidine was discontinued and granulocyte-macrophage colony stimulating factor was administered, with concomitant recovery of the granulocyte count and subsequent development of a leukemoid reaction. This leukemoid reaction was attributed to either infection or to a reaction to the G-CSF administration. The patient was treated with broad-spectrum antibiotics, but his condition deteriorated further and he died. The family declined an autopsy.

The patient's prior medical history includes a nephrectomy 40 years previously, chronic renal failure for 10 years on peritoneal dialysis, and severe exfoliative dermatitis suspected to have been due to an allergic reaction to erythropoietin treated with steroids several weeks prior to this admission. During that admission the patient had an attack of paroxysmal atrial fibrillation, and verapamil 40 mg twice daily was prescribed. In this patient, agranulocytosis developed 8 days after initiation of famotidine and discontinuation of pantoprazole.

Comment: The authors state that they cannot absolutely exclude the contribution of pantoprazole to the patient's blood dyscrasia, however they feel that famotidine caused the patient's disorder, and that a high dose of famotidine in the presence of renal failure may have resulted in a high famotidine level that increased the risk of drug toxicity. They also note that the half-life of famotidine is often increased in the elderly mainly due to an age-related reduction in kidney function. This reviewer agrees with their assessment.

WAES 0206USA01656 (Japan) A published article reported that a 48 year old female with secondary amyloidosis associated with systemic sclerosis (1988), Raynauds phenomenon, and reflux esophagitis developed pancytopenia, renal failure and cardiac failure while on therapy with famotidine for the treatment of ulcer. (dose and duration not reported). She developed cardiac failure and renal failure in December 1999, leading to hemodialysis. Her cardiac function recovered to normal but in _____, she suddenly exhibited cardiopulmonary standstill and died. The article mentioned that pancytopenia presumably due to the anti-ulcerative agent (famotidine) appeared early October, and that she recovered by administration of G-CSF and withdrawal of the drug.

Comment: It appears from the description that pancytopenia is possibly due to famotidine although the case presentation is sketchy.

WAES 86040737 (Japan) ALANINE AMINOTRANSFERASE INCREASED; ASPARTATE AMINOTRANSFERASE INCREASED; PYREXIA; HEPATIC FUNCTION ABNORMAL NOS; LEUKOPENIA NOS; RASH NOS; THROMBOCYTOPENIA A 70 year old female was hospitalized for hematemesis and was placed on cimetidine, and then changed to 40 mg famotidine on 11/30/85 for treatment of hemorrhagic gastric ulcer. Concomitant medication included Seven-E-P, Marzulene S, sucralfate, and primperan. She was on prior therapy with Tagamet. On 12/3/85, she developed a fever of 37.1C and developed erythema of the face, trunk, and extremities. Laboratory evaluation on _____ revealed SGOT 121 and SGPT 192. Famotidine was discontinued on 12/7/85. On _____ the patient's LDH increased to 587. Repeat laboratory evaluation on _____ revealed RBC count 409, hemoglobin 12.1, hematocrit 35.8, platelet count 85,000, WBC count 400 with bands 4, segmented neutrophils 18, eosinophils 4, monocytes 8, and lymphocytes 66. She was treated with prednisone, Decadron, cefmetazole, gentamicin, and venoglobulin I, IV fluid replacement, blood transfusions, and frozen plasma. Laboratory evaluation on _____ revealed RBC count 434, hemoglobin 12.8, hematocrit 38.5, platelet count 53,000, WBC count 200 with bands 23, segmented neutrophils 31, eosinophils 3, monocytes 3, and lymphocytes 40, SGOT 11, SGPT 42, LDH 237. On _____, the patient died from GI hemorrhage.

Comment: The adverse events could possibly have been caused by either famotidine and/or one of her other drugs.

WAES 01112446 A 72 year old hospitalized female developed interstitial nephritis, rash, dehydration and died while on therapy with famotidine. This was a case of suspected dermatomyositis in which the disease was complicated by hypersensitivity syndrome. The patient was HTLV-1 antibody positive and was hospitalized because of erythema and dermatophia in _____. During hospitalization, the disease was complicated by drug rash due to amlodipine besylate and interstitial nephritis due to famotidine. The patient was placed on therapy with famotidine for the treatment of chronic gastritis and gastric ulcer (dose and duration not reported). The report states that "erosion" developed over the entire body and she died of

high-degree dehydration in _____ Autopsy revealed B cell malignant lymphoma in the lung.

Concomitant suspect therapy included amlodipine besylate for the treatment of hypertension. Other concomitant therapy included warfarin potassium oxatamide, tansospirone citrate, chlorpheniramine maleate, ticlopidine hydrochloride, senna, azulene sulfonate sodium/L-glutamate, metildigoxin, and furosemide. On _____ the patient's BUN and serum creatinine were 19 mg/dl and 1.4 mg/dl, respectively. In May the patient's creatinine improved sharply upon discontinuation of the administration of famotidine. On _____ the patient's BUN and serum creatinine were 62 mg/dl and 3.7 mg/dl, respectively. On _____, the patient's BUN and serum creatinine were 36 mg/dl and 1.4 mg/dl, respectively.

Comment: According to the case report, the patient had an "erosive" (?denuding) skin reaction to amlodipine which caused dehydration and apparently led to the patient's death. The reporting physician stated that the causality of famotidine with interstitial nephritis was judged as unknown. In any case, the interstitial nephritis was not reported to be the cause for the patient's death.

WAES 01012379-- A 24 year old female with occasional alcohol consumption was placed on therapy with famotidine tablet (dosage, duration and indication not reported). Concomitant therapy included ranitidine, teprenone, metoclopramide and loxoprofen (dosages, durations and indications not provided) and prednisolone and methylprednisolone both for the treatment of Still's disease. In January 1996, the patient was seen by a physician for the development of a fever and erythema which did not abate. In _____, the patient was hospitalized in a clinic due to a worsening of the fever and erythema which at this time was accompanied by arthralgia. On _____, the patient was again hospitalized for a fever of unknown origin. It was reported that superficial lymph nodes were palpable, she was positive for Koebner's phenomenon (incidental finding), and a dispersed erythema was noted on both of her upper arms and on her right femur. Lab revealed an ESR of 129 and a WBC of 15000 with 21% bands. LDH was 842 with a serum alkaline phosphatase of 261 and a total bilirubin of 0.3. C-reactive protein was 4.6 mg/dL with a rheumatoid factor of < 191 IU/mL. At that time, the patient was diagnosed with adult onset Still's disease (AOSD) and was treated with prednisolone and pulse therapy with methylprednisolone and on an unspecified date, the patient's symptoms of fever, erythema and arthralgia abated.

Therapy with prednisolone was gradually reduced and it was reported that in approximately September 1996, the patient was noted to have developed a slight hepatopathy. Three months later in December 1996, the patient developed acute hepatitis-like hepatopathy without being accompanied by specific symptoms (laboratory findings not provided), which was reported to have abated spontaneously.

Then in _____, the patient had a relapse of fever and erythema so pulse therapy with methylprednisolone was again started. It was reported that although the symptoms of AOSD had begun to subside, severe hepatopathy appeared again and proceeded to fulminant hepatitis. Despite treatment and hospitalization the patient died. The cause of death was hepatic disorder and hepatitis. Therapy with famotidine, prednisolone, methylprednisolone, ranitidine, teprenone, metoclopramide and loxoprofen were suspected to be involved with the onset of hepatopathy.

Comment: Medication could have contributed to the patient's hepatic abnormalities. Any of several medications could possibly have been involved.

WAES 86040732--A 52-year-old hospitalized female with cervical cancer, lumbago, marasmus, and peptic ulcer was treated abroad with famotidine 40 mg daily, starting on 10/16/85. Concomitant medication included morphine 15 mg daily, cocaine 15 mg daily, Ludiomil 25 mg daily, and Atarax 50-100 mg daily. The patient was also on therapy with the following: teprenone, cefotetam, pentazocine, neutropin, stronger Neo-Minophagen C, methaphyllin, and sucralfate. On 10/31/85 she experienced confusion with visual hallucinations. Therapy with Ludiomil was discontinued on 11/1/85 and therapy with famotidine was discontinued on 11/3/86. On _____ laboratory analysis revealed BUN 28 and serum creatinine 2.0 (pre-study values: _____, BUN 35, creatinine 2.3) and her consciousness and behavior returned to normal. Subsequently on _____ the patient died due to cervical cancer.

Comment: The patient's symptoms resolved after discontinuing ludiomil and famotidine. Note that the patient's dose of famotidine was high considering that her creatinine was elevated.

WAES 88080392--A 76-year-old female with a history of chronic obstructive bronchitis, myocardial infarction, heart failure, diabetes mellitus, cholecystolithiasis, urinary incontinence, hyperuricemia, and insomnia was placed on therapy with Pepcid 40 mg daily, on 7/5/88 for the treatment of gastritis. Concomitant medications included levomepromazine, 10 mg daily, from 7/5/88 to 7/6/88 for the treatment of insomnia. Promazine hydrochloride, 3 ml/daily (total daily dosage not reported), was added to her treatment regimen from 7/11/88 to 7/12/88 for the treatment of insomnia. Additional concomitant medications included valeriane solution, digitoxin, spironolactone, furosemide, terbutaline sulfate, isosorbide mononitrate, homeopathic therapy, allopurinol, glybenclamide, and captopril. On _____ patient experienced hepatic coma. Laboratory evaluation revealed SGOT 4,114, SGPT 1,947, GGTP 340, LDH 14,511, glutamate dehydrogenase 2,666, hydroxybutyric dehydrogenase (HBDH) 3,171, serum bilirubin 2.35, and cholinesterase 3,503. Therapy with Pepcid was discontinued on 7/18/88. The patient's hepatic failure continued to progress, and the patient died on _____.

Comments: The etiology of hepatic failure in this patient is unclear since hepatotoxicity has been reported with use of promazine, furosemide, allopurinol, glybenclamide and captopril as well as famotidine.

WAES 89080641-- A 56 year old female, with gastroduodenitis, alcoholism, tachycardia, heart failure, ascites, edema and a history of hepatitis B was placed on therapy with famotidine 40 mg PO daily for the treatment of reflux esophagitis on 04SEP86 . Concomitant medication included furosemide/spironolactone, acetyldigoxin and sotalol HCl. On 30OCT86 the patient's cirrhosis worsened and that day therapy with famotidine was discontinued. On _____, the patient was hospitalized for weakness and abdominal pain, and on _____ the patient died due to renal failure and circulatory failure. The investigator felt that the patient's worsening cirrhosis was related to therapy with famotidine.

Comments: The patient's worsening cirrhosis could possibly be related to alcohol, drug, or history of hepatitis. The patient had pre-existing heart failure and the cause of death was reported to be circulatory and renal failure.

WAES 99100858 (Japan)-- A 72 year old female with a hepatic disorder, hyperlipidemia, gastritis, diabetes mellitus and complications of the diabetes mellitus (condition unspecified) and a history of a respiratory "inflammation" developed worsening hepatic function abnormality which lead to hepatic insufficiency which prolonged her hospitalization while she was on therapy with famotidine. Subsequently, the patient died. On 27-JAN-1999 while hospitalized

(rationale for hospitalization not provided) the patient was placed on therapy with famotidine tablet, 20 mg daily, for the treatment of a gastric ulcer. Concomitant therapy included voglibose, 0.6 mg daily, for the treatment of diabetes mellitus and pravastatin sodium, 10 mg daily, for the treatment of hyperlipidemia. Other concomitant therapies included gliclazide and ranitidine. While hospitalized, it was reported that the patient had developed "serious jaundice" and elevated LFTs. Laboratory findings at that time revealed a serum gamma-glutamyl transferase (GTP) level of 1000, a serum aspartate aminotransferase (SGOT) level of 200, a serum alanine aminotransferase (SGPT) level of 200, and a total serum bilirubin (TB) of 5. On 26-JUL-1999 therapy with famotidine, pravastatin sodium, and voglibose were discontinued. Other laboratory findings done during that time revealed that there were no reported viral diseases, tumors, cholelithiasis or autoimmune diseases found. Later the patient's bilirubin continued to rise up to 26.7 and hemodialysis was initiated. In _____ a liver biopsy revealed "marked cholestasis and bile duct injury". In _____ the patient developed hematemesis and shock and was transfused for a bleeding ulcer. The patient was treated for the hepatic insufficiency and circulatory failure and was eventually intubated and placed on antibiotics, and subsequently was hypotensive and went into cardiac arrest.

Comment: Many of her drugs could possibly have contributed to the patient's hepatic insufficiency. The patient later was treated for multiple problems including a bleeding ulcer, and ultimately had circulatory failure and went into cardiac arrest which caused her death.

WAES 88050390 (Italy)-- A 63-year-old male with a 15-year history of Parkinson's disease was placed on therapy with Pepcid, 40 mg daily, on 4/29/87 for the treatment of an endoscopically proven gastric ulcer. Concomitant medications included Sinemet (since 1972), amantadine and Citicolin. On approximately 7/15/87, the patient developed fever and anuria. He was treated with bromide and trihexyphenidyl HCl. The patient experienced septic shock and was hospitalized on _____. Laboratory evaluation revealed WBC count 1.9, neutrophils 52%, lymphocytes 45%, eosinophils 3%, BUN 1.22, creatinine 2.08 and ESR 25. Later that day, the patient died.

Comment: Famotidine may possibly have contributed to development of neutropenia. Other drugs may also have done this.

WAES 88020755 (US) A 70-year-old male was placed on therapy with Pepcid 40 mg daily (duration not reported), to treat a peptic ulcer. Concomitant medication included Carafate. While on therapy with Pepcid, he developed thrombocytopenia and subsequently bled to death.

Comment: Very little detail is provided to enable an assessment of this case. However, a health care professional did provide this information, so attribution will be left as a "possible".

WAES 88050012 (US)-- A 63-year-old male diabetic developed bone marrow depression with pancytopenia and subsequently died while on therapy with Pepcid 40 mg. Concomitant medications included Indocin (dosage and duration not reported), prednisone, Micronase, Mylanta, Xanax and Ser-Ap-Es. Laboratory evaluation on _____ revealed the platelet count decreased. The patient had developed profound leukopenia and was hospitalized. Pepcid was discontinued. On _____, the patient died from cardiac arrest, shock and possibly sepsis. The patient's history included osteoarthritis, hypertension, temporal arteritis, alcoholism and smoking.

The patient was admitted with polyuria, polydipsia and blood sugar of 969, serum ketones negative. Laboratory evaluation the day after admission revealed hematocrit 41.9, WBC count 7,100, platelet count 114,000, blood sugar 123, BUN 21 and serum alkaline phosphatase 154. The patient complained of dyspepsia and an upper GI endoscopy on _____ showed a large gastric ulcer. Therapy with Pepcid 40 mg daily and antacids was initiated at that time. On _____, repeat laboratory evaluation showed WBC count 1,900, hematocrit 34 and platelet count 49,000. The physician felt that the abnormalities might have been associated with Indocin and Pepcid, so these drugs were discontinued. The patient became hypotensive and was transferred to the ICU. A bone marrow biopsy on _____, showed hypoplastic bone marrow most consistent with aplastic anemia. Treatment with dopamine was initiated. A markedly elevated CPK was noted and the patient developed an erythematous, bullous rash. Blood cultures were taken and therapy with Cefazolin was started. On _____, the cultures grew Staph. aureus. That day, the patient developed ascites, asterixis and jaundice. A gastroscopy on _____ revealed a fresh clot in the distal stomach and that day the patient received four units of packed cells, ten platelet packs, and four units of fresh frozen plasma. The patient was later found to have a large gastric ulcer eroding into his pancreas and a subtotal gastrectomy was performed. He subsequently showed signs of ARDS, his sputum grew out Pseudomonas, his blood pressure dropped, he developed metabolic acidosis, went into cardiac arrest and died.

Comment: This case is confounded, but medications could have contributed to bone marrow depression.

WAES 89090148(Finland)-- A 79-year old female, with nausea, vomiting, diabetes mellitus, and small polyp-like abnormalities in the pylorus with suspected malignancy was placed on therapy with famotidine, 40 mg, daily for abdominal pain on 21MAR89. Concomitant medications included glibenclamide, meprobamate/quinine and melperone hydrochloride. On _____, leukopenia and thrombopenia were confirmed by laboratory analysis which revealed hemoglobin 87, WBC count 4,200 and platelet count 52,000 (pre-treatment laboratory analysis on _____ revealed hemoglobin 144, WBC count 12,900 and platelet count 78,000). On _____, repeated laboratory analysis revealed hemoglobin 95, WBC count 1,800 and platelet count 89,000 and therapy with famotidine was discontinued. On _____, hemoglobin was 105, WBC count 21,200 and platelet count 73,000. Pancytopenia was confirmed by laboratory analysis (exact test date unknown) which revealed hemoglobin 80, WBC count 1,100 and platelet count 33,000. Bone marrow biopsy was performed which revealed a suspected drug induced bone marrow depression. On _____, the patient died. An autopsy revealed cancer of the pancreas, no signs of metastasis, splenomegaly, bone marrow and lymph nodes were normal. Probable causes of death were the pancreatic carcinoma and bone marrow aplasia.

Comment: Many drugs she was taking could have contributed to the bone marrow suppression. The role of famotidine is unclear.

WAES 90060292(France)-- A 53 year old male with liver function abnormality related to sarcoidosis, portal hypertension, alcoholism, esophageal varices, and portocaval shunt, and splenectomy due to hemolytic anemia was placed on therapy with famotidine 40 mg PO daily for the treatment of a peptic ulcer on 11DEC89. Concomitant medications included lorazepam and corticosteroids. On 06JAN90, the patient developed mild hematemesis and, on _____, he was hospitalized. On admission, endoscopy revealed no hemorrhagic lesions and confirmed a healed duodenal ulcer. On 10JAN90, the patient became febrile 40°C and confused and had diarrhea.

Therapy with famotidine was withdrawn. On _____, the patient was transferred to the intensive care unit. Septic shock with signs of hypotension (SBP 70 mmHg), oligo-anuria, confusion, respiratory distress syndrome, and purpura of the legs was diagnosed. Laboratory analysis revealed WBC count 600, neutrophils 83, platelet count 21,000, and hemoglobin 8, serum creatinine 190, serum potassium 2.6, and prothrombin ratio 31%. A bone marrow examination revealed a "desert aspect of medular aplasia". Urine and blood cultures grew out Escherichia Coli. Antibiotic treatment with piperacillin, amikacin, ceftazidime, amoxicillin, and metronidazole was initiated. The patient was artificially ventilated, however, despite treatment on _____, the patient died. An autopsy revealed non-hodgkins lymphoma. The probable cause of death was identified as septic shock. The reporting physician felt that the patient's experiences were related to therapy with famotidine.

Comments: The patient's underlying medical problems including alcoholism and non-Hodgkins lymphoma that could have contributed to his bone marrow depression. The role of famotidine is unclear but is possible.

WAES 92090513 (Japan)-- A 39 year old female with bronchiectasis, lupus erythematosus and a 10-year history of episodes of fever and pneumonia (most recent episode 05NOV91) was placed on therapy with famotidine 20 mg PO daily for the treatment of upper abdominal pain on 15DEC91. Concomitant therapy included benproperine phosphate, carbocisteine, ambroxol hydrochloride, triazolam, sulbactam, cefoperazone, sennoside B, sucralfate, dicyclomine, aluminum hydroxide gel and magnesium oxide. Other concomitant therapy included ofloxacin, 300 mg, PO daily which was initiated on 11DEC91 (indication unknown). On _____, the patient presented with cough, fever, periocular purpura, skin rash on the cheeks and edema of the fingers, and she was hospitalized. Upon admission, laboratory analysis revealed a platelet count of 2000, hemoglobin 10.5 and WBC count was 500. Aplastic anemia was diagnosed. Pulsatile steroid therapy, antibiotics, G-CSF and daily transfusions of platelets (20 units daily from 06JAN92-11JAN92) was initiated and famotidine, ambroxol hydrochloride and triazolam were discontinued. On 22JAN92, paralytic ileus, myocardial ischemia and DIC developed. On _____, the patient became unconscious, her pupils were dilated, respiratory rate, heart rate and blood pressure fell and she died. The cause of death was identified as aplastic anemia. Thereporting physician stated "the aplastic anemia might be 1) idiopathic aplastic anemia, 2) an autoimmune disease, or might be related to 3) viral infection, or 4) drugs.

Comment: Because of confounders and a complex medical history, the role of famotidine in the aplastic anemia is possible, but unclear.

WAES 92095544 (Germany)-- A 64 year old male with severe cardiac and respiratory failure was placed on therapy with famotidine (dosage, form not provided). Concomitant medication included antibiotics. Subsequently, the patient developed neutropenia (WBC count 2100, neutrophils 462). The bone marrow aspirate demonstrated serious reactive alterations in the granulopoiesis and an enhanced presence of promyelocytes. After the withdrawal of famotidine, the patient received the same antibiotics in combination with pirenzepine. During this modified therapy the neutrophils increased to 4700. Twelve days after the recovery of neutrophils in the peripheral blood the patient died as a result of cardiac and renal failure.

Comments: The neutropenia was probably caused by famotidine since the patient's neutropenia improved while receiving the other medications that he had been taking.

WAES 92095548 (Germany) A 44 year old female was placed on therapy with famotidine (formulation and dosage not provided) for prophylaxis of ulcer following a polytraumatic traffic accident, splenectomy and partial resection of the liver. Concomitant medication included antibiotics. A few days later, laboratory evaluation revealed WBC count 22100 and neutrophils 19890. Bone marrow examination showed only reactive alterations. Nine days later, a second bone marrow aspiration was indicated because of a severe decrease of the granulocyte count in the peripheral blood (WBC count 1000, neutrophils 360). At the same time in the bone marrow disturbances of erythropoiesis were noticed, as well as agranulocytosis and reactive changes in both plasma and lymphocytes. After removal of the medication a pronounced rise of progenitors was detectable in the bone marrow while the severe neutropenia persisted in the peripheral blood (WBC count 400, neutrophils 32). Complete recovery of all hematopoietic parameters was not observed because of sudden death of the patient (cause of death unknown).

Comments: The agranulocytosis could possibly be related to famotidine, however other unidentified antibiotics could also be responsible.

WAES 92127270 (Sweden) A male of unknown age underwent an artificial heart valve and coronary bypass operation. Post-op the patient developed infections which had to be treated with large doses of antibiotics. He also developed a stress ulcer, which was treated with famotidine (total dose and duration not reported). Due to the artificial valve, the patient had to receive anticoagulants. Warfarin was used as the first choice. In spite of high doses of Warfarin the PoP-values (the prothrombin-proconvertin method) stayed at 60-70%. Antibiotics were discontinued without effect. Famotidine was discontinued, but at the same time warfarin was changed to dicumarol and the PoP-values went down to adequate levels (10%). The patient was later sent to Spain for convalescence. He did not follow his anticoagulation properly and developed an acute subdural hematoma, probably due to too strong anticoagulation. He had surgery in Spain and transported home. After treatment for two weeks at hospital, he died. The physician felt that the subdural hematoma and the death was not related to the earlier treatment with famotidine. The physician also felt that that the high PoP-values in spite of Warfarin was related to therapy with famotidine.

Comment: We cannot conclude from this case that famotidine was responsible for the elevated PoP. Famotidine's drug insert states that "No drug interactions have been identified. Studies with famotidine in man, in animal models, and in vitro have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine and antipyrine."

WAES 93020031(Japan)-- A case from a published article states that a 63-year old male was placed on therapy with famotidine (dosage not reported) in September 1988 for treatment of a gastric ulcer with symptoms dating back to 1978. Concomitant medication included cimetidine and sultamicillin and he was receiving blood transfusions. Subsequently his ulcer symptoms were controlled, but he experienced fever, rash and symptoms of liver function abnormalities. In June 1989 he presented with fever, rash, epigastric pain and dark stool. Therapy with famotidine and cimetidine were discontinued and therapy with dexamethasone (manufacturer unknown) was initiated and continued for two weeks. He was transferred to the authors' clinic on _____ On admission she had coalescing rash and papules over the trunk, erosion of mouth mucosa, liver function abnormalities, and pruritus. The WBC count was low and continued to decrease as part of pancytopenia. On the 4th hospital day, he developed dyspnea with wheezing with CT showing

focal bronchopneumonia. He did not respond to theophylline, b-adrenergic drugs, antibiotics, and globulins. Cefuzonam, cefotiam, fosfomycin, amikacin and moxalactam were used during the 2nd wk without effects. The patient required intubation and died on day 14 in respiratory failure. Autopsy showed *Candida pseudohyphae* filling bronchiole lumens and infecting pharynx, stomach, the bowels and kidneys. Lung parenchyma showed only focal bacterial pneumonia. Other findings included bone marrow aplastic anemia, cholestatic hepatitis and lymphocyte infiltration of periarterial areas of the skin, indicating drug-induced skin rash.

Comments: Drugs (famotidine among them) may have contributed to patient's skin eruption, liver function abnormalities, pancytopenia and ensuing events.

WAES 93071004 (US)-- A 20 year old female ingested famotidine and nortriptyline (dosages unknown) in a suicide attempt. The patient was taken to the ER 3 hours postingestion semi-comatose with a tachycardia of 120. "Gastric decontamination" was performed and the patient was placed on a ventilator. She was subsequently admitted to the hospital and treated with pancuronium bromide, midazolam hydrochloride, multiple doses of activated charcoal, and IV sodium bicarbonate. Sinus tachycardia persisted and EKG revealed prolonged QT interval. On the second day postadmission, patient developed pulmonary edema and ARDS and died 8 days later.

Comment: The patient died from a suicide attempt. The drug more implicated in this death is likely to be nortriptyline since patient exhibited tachycardia and a prolonged QT interval. Respiratory depression, aspiration and ARDS may also complicate severe overdoses of nortriptyline.

WAES 93121150 (Japan)-- A 72 year old female with 'insulin resistant' diabetes mellitus, chronic urticaria, bronchial asthma, mild hepatic disease and an unspecified hypersensitivity to unspecified drugs, was placed on therapy with famotidine 40 mg daily on 09SEP93 for prophylaxis against steroid-induced gastrointestinal ulceration. Prior therapy included famotidine 40 mg daily from 05NOV92 until 22JUL93 with no noted problems. Concomitant medication included prednisolone 10 mg daily initiated in November 1992 for treatment of bronchial asthma and chronic urticaria; glibenclamide (Daonil) 5 mg daily initiated on 08SEP93 for treatment of insulin resistant diabetes mellitus, and metildigoxin (Lanirapid) 50 mcg daily initiated on 11SEP93 for treatment of mild cardiac failure. On 15OCT93 treatment with famotidine, prednisolone, glibenclamide and metildigoxin were all discontinued. On 16OCT93 the patient developed a sudden fever of 38.5 degree Celsius rising to 39.6 degree Celsius on 17OCT93. Laboratory evaluation on _____, revealed hemoglobin 9.4, hematocrit 27.6, platelet count 101000, WBC count 2000, bands 2%, eosinophils 18%, monocytes 3% and lymphocytes 77%. Treatment was initiated with intravenous hyperalimentation, cefazolin 2g daily, methylprednisolone sodium succinate-benzylalcohol (Solu-Medrol) 250 mg and human plasma protein fraction (Plasmanate). The patient also developed symptoms of hyperthermia, nausea, vomiting and abdominal pain. A chest x-ray was normal. Repeat tests on _____ were worse and revealed hemoglobin 8.8, hematocrit 25.1, platelet count 54000, WBC count 600, bands 0%, eosinophils 1%, monocytes 8%, lymphocytes 90%, atypical lymphocytes 1% and total serum bilirubin 5.45. Treatment was initiated with lenograstim (injection Neutrogen) 100 mcg on 19OCT93. After midnight, the patient's blood pressure "dropped". She subsequently responded to treatment with dopamine hydrochloride. Repeat tests on _____ revealed hemoglobin 8, hematocrit 22.6, platelet count 4.9, WBC count 400, segmented neutrophils 2%, bands 1%, eosinophils 1%, monocytes 7%, lymphocytes 85%, atypical lymphocytes 4% and total serum

bilirubin 6.16. On _____ the patient's condition rapidly deteriorated. She died on the same day. The cause of death was reportedly due to agranulocytosis and disseminated intravascular coagulation (DIC). A postmortem examination was not performed. The reporting physician felt that the patient's experience was a "case of drug-induced agranulocytosis due to famotidine". Prednisolone, glibenclamide and metildigoxin were considered to be secondary suspect therapies.

Comment: This pancytopenia may have been drug induced, however there is more than 1 suspect drug.

WAES 94051343(US)-- A 64 year old West Indian female with end stage renal disease, cardiomyopathy, chronic cholecystitis, chronic pancreatitis, pneumonia, septic shock, an AV graft of the right arm and an allergy to penicillin was placed on therapy with famotidine 40 mg daily for the treatment of a duodenal ulcer in 1994. Medical history included coronary artery disease, an MI and a CVA. Concomitant medications included enalapril maleate(MSD) 10 mg daily for the treatment of hypertension, amiodarone, dipyridamole, multivitamins, calcium acetate, propoxyphene napsylate-acetaminophen (Darvocet-N 100), erythropoietin, vancomycin, acetaminophen and iron dextran injection. On 16MAY94 the patient was noted to have thrombocytopenia. The patient received 6 units of platelets on _____, 6 units on _____ and 6 units on _____. At that time therapy with famotidine, enalapril, and amiodarone was discontinued. The patient received a total of 30 units of platelets over a course of 14 days. The platelet level "really did not rise." On 21MAY94 the patient was treated with ciprofloxacin (Cipro) and omeprazole (Prilosec). That same day the patient experienced elevated S-T segment in the V5 and V6 leads and was transferred to the cardiac care unit. On _____ her platelet level rose to 118,000. On _____ the patient developed cardiorespiratory arrest and died. {possible}

Comment: The patient was on several drugs that could have contributed to thrombocytopenia. She had a history of cardiomyopathy and apparently had a myocardial infarction and died from that.

WAES 94060865 (Japan)-- A 77 year old male patient with pulmonary emphysema, asthma, bronchitis, hypertension and who was susceptible to respiratory tract infections was placed on therapy with famotidine 20 mg bid on 25OCT93 for treatment of gastritis. Concomitant therapy included theophylline, erythromycin stearate, nifedipine, sparfloxacin and pronase (Empynase PD). On 15JAN94, the patient developed a cough with sputum, fever and pain in the right side of his chest. He was hospitalized on _____ and all medications were discontinued. Chest x-ray revealed right lobar pneumonia. Laboratory evaluation on _____ revealed red blood cell count (RBC) 4,360,000, white blood cell count (WBC) 1000, SGOT 32, serum alkaline phosphatase 63, LDH 266, BUN 51.2, PCO2 38 mm/Hg and PO2 46 mmHG (prior laboratory evaluation on 18AUG93 revealed RBC 4,620,000, WBC 5600 and SGOT 25). The patient received unspecified antibiotics; however, the symptoms did not improve. On 18JAN94 the patient developed sepsis and "multiple organ failure". Repeat laboratory evaluation on _____ revealed RBC 3,910,000, platelet count 101,000, WBC 2600, SGOT 3574, SGPT 800, BUN 71, serum creatinine 3.5, serum potassium 6 and serum chloride 94. The patient subsequently died on _____ of severe pneumonia, leukopenia and multiple organ failure.

Comment: Medications may have contributed to the patient's leukopenia.

WAES 95056081(France)-- A 66 year old male patient with history of arteritis in the lower limbs experienced abdominal pain and vomiting, and was placed on therapy with famotidine

TAB PO 20 mg twice a day on 03-APR-95 . Concomitant therapy included phloroglucinol, nifuroxazide, metoclopramide, aluminum OH /magnesium OH and acenocoumarol. On 04-APR-95 the patient experienced mild hematemesis. Late in the evening, he experienced shock followed by coma and cardiac arrest at home. Cardiac massage led to resuscitation and the patient was transferred to hospital ICU. Diagnosis was that of intestine infarction (responsible for abdominal pain) and severe coagulation disorder (prothrombin ratio below 10%). Despite intensive care, death occurred one hour after admission (on _____). The causes of death were shock and coagulation disorder. Autopsy confirmed bowel infarction (small intestine necrosis on about 30cm) and diffuse hemorrhage mainly in lungs .

Comment: The patient had a bowel infarction. We do not have enough details about this case. It is not clear what caused the patient's coagulation disorder. The patient could have been septic with DIC secondary to the infarcted bowel. We don't know anything about his nutritional status which could affect his vitamin K levels and subsequently his coagulation. He was also placed on several new medications in addition to famotidine so an attribution of a specific drug interaction between acenocoumarol and a particular medication cannot be made. Acenocoumarol is generally not available in this country, but is prescribed elsewhere. However warfarin is, and the drug insert for famotidine states that studies with famotidine in man, in animal models, and in vitro have shown no significant interference with the disposition of warfarin.

WAES 95120670 (Japan)-- A 69 year old female with cerebral infarction, eosinophilic pneumonia, gastritis and a history of three hospital admissions in 1994 for suspected eosinophilic pneumonia developed cerebral thrombosis on 31AUG95 . The patient was treated in the acute stage with ozagrel sodium (Cataclot) and IVH. Right hemiplegia and dysarthria persisted. Ground glass opacity detected in the left lung disappeared when steroid pulse therapy was performed. On _____ baseline laboratory evaluation revealed a platelet count of 29.8. On 18SEP95, the patient's disease was considered to be in "a chronic stage" and bed rest accompanied by therapy with indeloxazine HCL (Elen) and dihydroergotoxine mesilate (Lysergin) was initiated. No hematological examination was performed. On 02OCT95 the patient was placed on therapy with famotidine, tab for the treatment of gastritis. Concomitant therapy included digestive enzyme, rebamipide, and ceftazidime. Other concomitant therapy included methylprednisolone. On _____ the patient was examined and anemia was suspected. Hematological examination was scheduled for the following day. On _____ the patient developed advanced thrombocytopenia with a platelet count of 4,000. On _____ a platelet transfusion (20 units) was given. On _____ , the platelet count declined to 2,000. ITP was suspected and Venoglobulin-I (15g/day) was initiated. on _____ , platelet transfusion (30 units) was given. Subsequently, the patient developed bloody stools, he began to groan and ST elevations in II and III leads on ECG were noted. The patient then developed cardiopulmonary arrest and died. The direct cause of death was a suspected myocardial infarction.

Comment: Medications could have contributed to the thrombocytopenia.

WAES 96061008(Japan)--74-year-old female was hospitalized for a consciousness disorder following a subarachnoid hemorrhage. She also had mild hepatic disturbances, anemia, constipation, hypertension, and reflux esophagitis. She was placed on therapy with famotidine, tab, 20 mg, twice a day for the treatment of upper gastrointestinal bleeding on 19FEB96. Concomitant therapy from 30OCT95 to 07MAY96 included zonisamide ("Excegran"), 200 mg total daily dose for the treatment of epilepsy. Other concomitant therapy included benexate hydrochloride betadex, magnesium oxide, domperidone and cisapride. On 12APR96, the patient

developed pancytopenia, which was considered to be life threatening. On 22APR96 therapy with famotidine was discontinued. On 07MAY96 therapy with zonisamide was discontinued. Except for a favorable response to blood transfusion, the patient did not respond to any treatment after discontinuation of therapy and she died on _____. Probable causes of death were reported as respiratory failure and renal failure. In follow-up, the physician provided laboratory evaluation which revealed RBC 245, Hb 9.3, Ht 26.6, PLT 35 and WBC 3800 on _____ RBC 142, Hb 5.8, Ht 16.8, PLT 17.3 and WBC 3000 on _____. RBC 257, Hb 8.5, Ht 24, PLT 1 and WBC 2200 on _____ RBC 179, Hb 5.8, Ht 16.5, PLT 6.5 and WBC 5200 on _____ and RBC 230, Hb 7.2, Ht 20.5, PLT 3.8 and WBC 2300 on _____. The physician commented that "pancytopenia was a major cause of death, although the degree of respiratory failure and renal insufficiency (presence of thrombosis, hemorrhage and other hematological disturbances) and myelogram was unknown since there was no autopsy. Famotidine was strongly suspected but zonisamide was also given at the same time".

Comments: Drugs could have played a role in immunosuppression, however there were multiple drugs and anemia and thrombocytopenia existed prior to starting famotidine therapy. From the case report, it is not clear why the patient went into respiratory and renal failure.

WAES 98012543 (Japan) A 71 year old female was placed on therapy with famotidine, tablet, 20 mg, twice a day for the treatment of gastric ulcer on 09-FEB-1997. Concomitant therapy included tegafur, 150 mg daily, for the treatment of "rectal cancer." Both of these drugs were started status post a "radical operation" for rectal cancer. Other concomitant therapy included brotizolam, lactobacillus acidophilus, sofalcone, teprenone, and magnesium oxide. Two weeks after the start of famotidine, the WBC count was noted to be 3000. After the start of tegafur on _____ the white blood cell count increased from 3500 to 4200. On _____ the patient was discharged from the hospital in favorable condition. Follow-up labs done on _____ revealed a white blood cell count of 3700 and platelets were 14.7. On _____ the white blood cell count was 2900, platelets were 13.3 and the red blood cell count was 365. On 19-Sep-1997 therapy with famotidine was discontinued because the white blood cell count had fallen below 3000. On 15-Nov-1997, purpura and intraoral hemorrhage were observed. Retinal hemorrhage was reportedly observed at another ophthalmologic clinic. On _____ the patient was examined at the outpatient clinic. Although no other symptom other than purpura was observed, the white blood cell count was 700, the red blood cell count was 241, and the platelets were 0.1. It was reported that "since pancytopenia with a bleeding duration exceeding 20 minutes was observed, the patient was immediately admitted for treatment." The treatment regimen included platelet administration, Glovenin and G-CSF administration, and Unasyn was also given. Despite all efforts, the patient died. The reporting physician felt that pancytopenia was "probably" related to therapy with famotidine.

Comment: This patient was ill with rectal cancer and had received chemotherapeutic agents in the past. It is unclear what effect the other concomitant medications may have had on the patient's hematologic parameters so it is difficult to make a probable attribution of the pancytopenia in this case.

WAES 98085518 (Germany)--A 76 year old male had hypertension, hyperuricemia, polymyalgia rheumatica and a history of myocardial infarction and aortocoronary bypass surgery. He was on therapy with furosemide/spironolactone 40 mg, daily for the treatment of renal insufficiency. On 31-DEC-97, the patient experienced persisting generalized pruritus. On 02-JAN-98, he developed a small-spotted exanthema. Between _____

patient was hospitalized for acute duodenal ulcer. Upon discharge from the hospital, therapy with furosemide/spironolactone was interrupted. On 21-JAN-98, furosemide 40 mg, daily was initiated for the treatment of renal insufficiency. On 29-JAN-98, therapy with furosemide was interrupted. On _____, the patient was hospitalized because of the exanthem. That same day, he was placed on therapy with clemastine hydrogen fumarate, tab for the treatment of pruritus (dose unknown) and prednisolone, tab, 50 mg, daily for the treatment of exanthema. On _____, the patient's skin change had paled and he was discharged from the hospital; therapy with clemastine hydrogen fumarate was discontinued and prednisolone was interrupted. That same day, the patient was placed on therapy with famotidine tab, for the treatment of duodenal ulcer (dose unknown). Prior therapy included methylprednisolone and nifedipine, and concomitant therapy included benazepril hydrochloride and lansoprazole. On 05-FEB-98, therapy with furosemide and prednisolone was restarted. On 11-FEB-98, the patient developed weeping skin changes of his lower arms. That same day, all medication was discontinued. On _____, he was hospitalized with aggravated exanthema and blisters on his back. He was diagnosed with Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (TEN). On _____, the patient died of worsening of the preexisting renal insufficiency and Stevens-Johnson syndrome. The reporting physician felt that the Stevens-Johnson syndrome/TEN was possibly related to therapy with famotidine, furosemide/spironolactone, furosemide, clemastine hydrogen fumarate and prednisolone. He did not rate the drug relationship concerning worsening of renal insufficiency.

Comment: The patient was on several medications that could be the cause of the Stevens-Johnson syndrome, and his exanthem may have begun prior to his therapy with famotidine. Thus it is unlikely that famotidine caused this event.

WAES 98100039 (Japan)-- An 88 year old female on long term bedrest with hypertension, congestive heart failure, thalamic hemorrhage and bronchitis on 24-JUN-1998 was changed from therapy with ranitidine HCL(Zantac) to therapy with famotidine, tablet, 40 mg for the treatment of gastric ulcer. Concomitant therapy included enalapril maleate(manufacturer unknown), furosemide and manidipine diHCL. The patient's urinary output was 2000-3000 ml/day. On _____, serum creatinine=0.5 mg/dl. Subsequently on _____, serum creatinine increased to 0.7 mg/dl and on _____, serum creatinine=0.9 mg/dl, NA=135 meq/l and K=7.6 meq/l. Analyzed arterial blood gas: ph=7.263, PaCO2=32.6, PaO2=126, HCO3=14.2, BE= -11.4, Cl=114 and "ABF lowered to 5.2." Since hyperchloremic metabolic acidosis was detected, "Meylon" was administered by a drip infusion. On 14-JUL-1998, therapy with famotidine was discontinued. Subsequently on _____, urinary N-acetyl-beta-D-glucosamidase(NAG) level was as high as 34.9 U/gCre. The reporting physician stated the symptom is quite likely renal failure and acidosis due to uriniferous tubular insufficiency. On _____ urinary output decreased to 1,340 ml/day. Furosemide was initially administered depending on urinary output. On 24-JUL-1998, therapy with vancomycin was ordered for bronchitis of methicillin resistant staph aureus (MRSA). On 26-JUL-1998, dopamine HCL (Inovan) was initially administered. Arterial blood gas on _____, ph=7.295, PaCO2=39.7, HCO3=18.7 and BE= -6.7. Urinary output was 425 ml/day. Furosemide was injected intravenously at six-hour intervals. No increase noted in urinary output despite increase of therapy with dopamine HCL. On _____, serum creatinine=3.7. On _____, the patient was discharged at the family's request. On _____, the patient died. The reporting physician felt that after therapy with ranitidine(Zantac) was changed to therapy with famotidine, the patient developed renal insufficiency and hyperchloremia acidosis. The physician stated that

the patient's acidosis disappeared after famotidine was discontinued. "Since serum creatinine levels rose and urinerous tubular disturbances appeared after initial famotidine administration, famotidine is considered to have triggered the onset of renal failure."

Comment: Worsening renal function could have occurred because the patient was getting septic from an infection with MRSA. She also had a history of hypertension and congestive heart failure, both of which could have contributed to her condition. The reporting physician stated that the acidosis disappeared after famotidine was discontinued and he considered famotidine to have triggered the onset of renal failure.

WAES 99041000 (Japan)-- A 72 year old female patient developed pneumonia, leukopenia, thrombocytopenia, hematoma, disseminated intravascular coagulopathy, respiratory failure and was hospitalized and died while on therapy with famotidine. On 23-OCT-1998 the patient with vasculitis, gastric ulcer, fever, dialysis, cataract, hepatic disorder, glomerulonephritis and antineutrophil cytoplasmic antibody was placed on therapy with famotidine tablets, 20 mg daily for the treatment of gastric ulcer. Concomitant therapy included methylprednisolone (Medrol), azosemide, teprenone, cefazolin na, methylprednisolone 21-succinate na, pranoprofen, "Tarivid" and betamethasone. On _____ the platelet count was 235,000. On _____, the platelet count was lowered to 116,000. On 11-NOV-1998 therapy with famotidine was discontinued. On _____ the patient's platelet count was 47,000 and 10 units of platelets were given. On _____, the platelet count was 6000. On _____ the platelet count was 55,000. On 30-NOV-1998 the patient developed an "abdominal straight muscular hematoma" which had appeared at rest. The patient received 20 units of platelets. On _____ the patient's platelet count increased to 87,000. On 04-DEC-1998 the patient developed diffuse pneumonia in both lungs and disseminated intravascular coagulopathy. Therapy with "Foy", 2 g was started. On _____ the patient's platelet count was 120,000. The patient died from recurring pneumonia and acute respiratory failure on _____. The reporting physician felt that thrombocytopenia and leukopenia were considered life threatening.

Comments: Medications, famotidine among them, may possibly have contributed to the thrombocytopenia. WBC values were not documented in the report.

WAES 99120864 (Japan)-- An 87 year old hospitalized female patient with renal insufficiency, rapidly progressing gastritis (treated with steroids), hypertension, anemia, and pseudomembranous enterocolitis was placed on therapy with famotidine, tablet, 20 mg daily for the treatment of gastric erosion and gastric ulcer on 13-NOV-1999. Concomitant therapy included furosemide, nisoldipine (Baymycard), "mosapride citrate", benzbromarone, ferrous citrate, prednisolone, propiverine HCl, amlodipine besylate (Norvasc), methylprednisolone, and vancomycin. On _____ the patient's platelet count, blood urea nitrogen (BUN), serum creatinine, serum aspartate aminotransferase, serum alanine aminotransferase, serum alkaline phosphatase, serum lactate dehydrogenase, and serum gamma-glutamyl transferase were 25.4×10^4 , 44 mg/dl, 3.2 mg/dl, 10 mg/dl, 5 IU/L, 130 IU/L, 242 IU/L, and 4 IU/L respectively. On _____ the patient developed thrombocytopenia and worsening renal insufficiency. On this same day the patient's platelet count, BUN, and serum creatinine were 8.5×10^4 , 145 mg/dl, and 7.3 mg/dl, respectively. On 02-DEC-1999 therapy with famotidine was changed from oral to intravenous administration. This therapy with famotidine was discontinued after one day. On _____ the patient's platelet count, BUN, and serum creatinine were 3.2×10^4 , 132 mg/dl, and 6.1 mg/dl, respectively. The patient was treated with a platelet transfusion and her platelet count increased to 30,000 (date not specified). On _____ the patient developed hepatic function

abnormality. On this same day the patient's laboratory values were as follows: serum aspartate aminotransferase 723 mg/dl, serum alanineaminotransferase 935 IU/L, serum alkaline phosphatase 1,265 IU/L, serum lactate dehydrogenase 483 IU/L, and serum gamma-glutamyl transferase test 334 IU/L. On _____ the patient's platelet count, BUN, and serum creatinine were 1.1×10^4 , 117 mg/dl, and 5.2 mg/dl. The patient was treated with Stronger Minophagen C from 07-DEC-1999 to 12-DEC-1999. On _____ the patient's platelet count recovered to 30.6×10^4 . The patient's lab values were BUN 116 mg/dl, serum creatinine 4.6 mg/dl, serum aspartate aminotransferase 34 mg/dl, serum alanine aminotransferase 203 IU/L, serum alkaline phosphatase 603 IU/L, serum lactate dehydrogenase 485 IU/L and serum gamma-glutamyl aminotransferase 140 IU/L, respectively. On _____ the patient died secondary to renal insufficiency. The outcome of the hepatic function abnormality was not reported.

Comment: Several medications could have caused the thrombocytopenia or hepatic function abnormality.

WAES 90021129 (Germany) PNEUMONIA NOS; BACTERIAL SEPSIS; CARDIAC FAILURE CONGESTIVE; GENERAL SYMPTOM NOS; JAUNDICE NOS A 51 year old male with heart failure, cardiomyopathy, hypertension and a history of myocardial infarction was placed on therapy with famotidine on 19JAN90 for the treatment of a ulcer (dosage unknown). Concomitant therapy included captopril, furosemide, isosorbide mononitrate and metildigoxine. In _____ the patient experienced malaise and became subicteric. He was consequently hospitalized and diagnosed with left-side pneumonia and right heart failure. On 24JAN90, therapy with famotidine was discontinued, and was replaced by ranitidine. Ampicillin was added to the patient's treatment regimen. Initially, the patient's condition improved, but then deteriorated. The patient's jaundice worsened, and after approximately 10 days of hospitalization, the patient died. A final abdominal ultrasonography revealed fields of increased echodensity which were not present at the time of admission. The chief physician felt these findings were a consequence of septicemia. Both the reporting and chief physicians felt that the patient's experiences were probably not related to therapy with famotidine.

Comment: The time sequence of events is not clear from the report and the reporting physician felt the adverse events were not related to therapy with famotidine.

WAES 88060294--(US) --A 67 year old male was treated with 20 mg famotidine for epigastric pain. He became confused, famotidine was discontinued, and he later developed grand mal seizures. He subsequently died and autopsy showed herpes encephalitis.

Comment: These events should not be attributed to famotidine.

WAES 97051979(Japan)-- A 69 year old male had angina pectoris with apical ischemia, hemorrhoids and a history of spondylolisthesis. "Herbesser" was administered and the patient's clinical course became uneventful. On 22MAR97, the patient complained of stomachache due to the stress of heavy work loads. Gastric camera examinations revealed severe erosive gastritis and therapy with famotidine, tab, 40 mg, daily was initiated. Concomitant therapy included diltiazem, teprenone, kolantyl, "coli-antigen-hydrocortisone", polaprezinc (Promac) and posterisan forte. On the evening of _____ after dinner, at 20:30, he collapsed. Cardiopulmonary arrest was confirmed by a relative who was a member of a paramedical staff. The patient was then transferred to an emergency ward of a hospital while cardiac resuscitation was being performed. The heart beat was recovered by cardiac resuscitation. On _____, after three days of hospitalization, the patient died of multiple organ insufficiency at 2:30. "In view of

the circumstances at the onset, cardiopulmonary arrest due to arrhythmia was suspected." However, no findings as to cardiopulmonary arrest in cephalo-computerized tomography, ECG, echocardiography, etc. were recognized after admission. The patient was entirely unaware of his symptom. He was a _____ who continued strenuous training. Physician's comments included . The causal relationship remained unknown because there were no findings as to ECG (such as extended QT) prior to the onset of the symptoms". Incidentally, serum concentration of famotidine was reportedly 28.8 ng/ml.

Comment: The physician stated that "famotidine's relationship with cardiopulmonary arrest was suspected because the symptoms, such as angina pectoris, appeared to be stable" However, this patient had preexisting cardiac disease and was under increased stress. An arrhythmia due to his underlying heart disease is more likely.

WAES 0206USA01643 (Japan)-- A 55 year old male outpatient had serious heart failure, ventricular extrasystoles, moderate premature ventricular contractions from 1989, pollen allergy, mild fatty liver and mild gastric polyp from 13-MAY-2002, and a history of adverse reactions due to disopyramide, pilcainide HCl, and other unspecified drugs. No abnormality was found in coronary arterial imaging in 1996. On 13-MAY-2002, the patient was placed on therapy with famotidine, tablet, 20 mg, once a day for reflux esophagitis. Concomitant suspect therapy included losartan potassium 25 mg daily from 07-JUN-2000 to 09-JUN-2002 for hypertension. Other concomitant therapy included metoprolol tartrate. On approximately _____, a Holter ECG showed ventricular premature contraction of 3803/d including couplets of 21/d. He had complete right bundle branch block. The St-T was not assessable (no marked change) and there was no QT prolongation. Blood pressure was relatively stable at 115/58-169/76, with a mean of 130/93. On _____ he was totally normal until finishing supper. After supper at 19:30 on _____, the patient collapsed and lost consciousness at home. A family member in the next room heard him having an abrupt onset of coughing and was found collapsed forward in a sitting position on the floor in front of the television with the belt of a blood pressure manometer binding his arm. At 20:00, an ambulance arrived, and the patient was in cardiopulmonary arrest. Ventricular fibrillation was observed by a monitor. Immediately, defibrillation was applied. At 20:25, he arrived at the hospital in cardiopulmonary arrest. Cardiopulmonary resuscitation failed to save his life. The patient died at 21:05 on _____. The cause of death was serious heart failure due to arrhythmia. The patient's physician reported that although the holter ECG was more stable than before, probably his condition worsened acutely.

Comment: This patient with a history of CHF and PVCs apparently died of an arrhythmia. A Holter done on famotidine was apparently not worse than usual. This death should not be attributed to famotidine

WAES 87060466 (US)-- An 88 year old female nursing home patient, with a history of senile dementia, hiatal hernia and allergy to penicillin, was placed on therapy with Tagamet for chronic peptic ulcer. On 5/21/87, Tagamet was discontinued and patient was placed on therapy with Pepcid 20 mg hs. Concomitant medication included Artane, Theragran-M, Dyazide, digestive enzyme, Ferro-Sequels, zinc sulfate and Neosporin. On 5/24/87, the patient developed a bluish coloration of the skin. A few days later, the patient developed swelling of her mouth and tongue. Pepcid was discontinued on 5/26/87. On 6/1/87, the patient developed cold symptoms, low-grade temperature and "upper respiratory problems." She was treated with Tylenol and

moved to an acute care unit. Benadryl and Solu-Medrol were added to her treatment regimen. The patient subsequently experienced cardiorespiratory arrest and died on _____

Comment: The patient may have had a hypersensitivity reaction to famotidine. It is also possible this reaction could have been due to another medication she was taking.

WAES 0304USA01607 PANCYTOPENIA; APLASTIC ANAEMIA (Japan) An 86 year old male inpatient with rectal cancer, mild atrial fibrillation, mild impairment of sinus function, haemorrhoids who was a cigarette smoker (20 cigarettes/day) was placed on therapy with famotidine, orally disintegrating tablet, 40 mg, daily for the treatment of gastric ulcer and gastritis on 09-FEB-2003. The dose was decreased to 20 mg daily on 15-Feb-2003. Secondary suspect therapy included aprindine hydrochloride 40 mg daily for the treatment of atrial fibrillation started on 22-Feb-2003. The dose of aprindine was increased to 60 mg daily on 08-Mar-2003. Other concomitant therapy included dipyridamole, isosorbide dinitrate, ferrous SO₄, levofloxacin, naftopidil, Bifidobacterium bifidum (LAC-B) and Mg oxide. The patient was not administered an anticancer drug. On 03-APR-2003, the patient experienced fever and a decreased white blood cell count. On 04-Apr-2003, therapy with famotidine and aprindine hydrochloride was discontinued. From 04-Apr-2003 until 06-Apr-2003, freeze-dried sulfonated human normal immunoglobulin (VENILON-I) was administered to treat the fever. Dosing with filgrastim (GRAN) at 75 ug/day was also initiated for the treatment of leukopenia. On 07-Apr-2003, the patient developed thrombocytopenia. The filgrastim dose was increased to 150ug/day to treat the leukopenia. On _____ a platelet transfusion was initiated. On 13-Apr-2003, filgrastim was increased to 300ug/day for treatment of leukopenia. On 14-Apr-2003, there was decreased blood pressure and deterioration of breathing. The patient was intubated and began receiving artificial respiration. On _____, at 4:37 PM, the patient died. The cause of death was infection, bleeding tendency, and anemia associated with pancytopenia. The reporting physician indicated that the probability of famotidine involvement is considered strong. The onset of the event was sudden. As there were no warning signs, drug involvement is regarded as the most likely explanation. The course of events (leukopenia>agranulocytosis>thrombocytopenia) suggests drug induced aplastic anemia." Famotidine "is regarded as the most likely cause of the adverse event, but the possibility of involvement by aprinine hydrochloride, which was administered around the same time, cannot be dismissed.

Comment: The pancytopenia is probably drug induced.

WAES 0212USA00620 DISSEMINATED INTRAVASCULAR COAGULATION; CEREBRAL INFARCTION; DRUG LEVEL NOS INCREASED; MULTI-ORGAN FAILURE; SEPSIS NOS; DYSKINESIA; DEPRESSED LEVEL OF CONSCIOUSNESS (Japan) A 55 year old hospitalized female with renal failure chronic (requiring hemodialysis), myelodysplastic syndrome, hepatic damage, hyperphosphatemia, insomnia, constipation, angina pectoris, pneumonia and lichen planus who on 02-JUN-2000 was placed on therapy with famotidine, tablet, 20 mg, once a day for the treatment of a gastric ulcer. Concomitant therapy included nifedipine, calcitriol, niceritrol, calcium carbonate, epinstine hydrochloride, zopiclone, sennoside, isosorbide dinitrate, nicorandil, and cefotiam hydrochloride. On _____ the patient's laboratory values were: hemoglobin 10.4 g/dl, hematocrit 32.9%, platelet count 5.6, white blood cell count 16000 /mm³, serum sodium 139 meq/l, serum potassium 5.4 meq/l, serum chloride 102 meq/l, BUN 102 mg/dl, and serum creatinine 13.7 mg/dl. Subsequently, the patient developed severe sepsis. On 04-DEC-2002 the patient experienced disturbed consciousness,

disorientation and tic-like involuntary movements. On the same day, the patient unconsciously took off her clothes. An elevation in the blood level of famotidine was suspected. On 04-DEC-2002 therapy with famotidine was discontinued. On 06-DEC-2002 the disturbed consciousness and involuntary movements improved after discontinuation of famotidine. On 07-DEC-2002 the patient had a severe cerebral infarction. By 09-DEC-2002 the patient developed severe sepsis which developed into DIC. On _____ the patient's laboratory values were: hemoglobin 10.4 g/dl, hematocrit 32.9%, platelet count 0.3, white blood cell count 13200 /mm³, serum sodium 152 meq/l, serum potassium 5.4 meq/l, serum chloride 117 meq/l, BUN 127 mg/dl, and serum creatinine 10.52 mg/dl. On _____ the patient died secondary to DIC with a complication of cerebral infarction. On _____ the patient's famotidine blood serum level was reported as 327.6 ng/mL (blood drawn on _____).

Comment: This patient had chronic renal failure, myelodysplastic syndrome, hepatic damage and was on multiple medications with a creatinine of 13.7 mg/dL. She experienced disturbed consciousness, disorientation and tic like movements when she had a high famotidine serum level; these symptoms improved when famotidine was discontinued.

WAES 0303USA01690 -- PANCYTOPENIA; DISSEMINATED INTRAVASCULAR COAGULATION; BONE MARROW DEPRESSION NOS The patient is an 86 year old female with a history of subarachnoid hemorrhage. (In _____, she underwent a surgical operation and on _____ she was admitted for rehabilitation.) On 03-OCT-2002, fecal blood was detected. On _____, the patient underwent a colonofibroscopy. A Borr type 2 tumor was detected in the cecum. The pathological data reported an adenocarcinoma. The patient was transferred to the Surgery Department. On _____, a colectomy was performed. On _____, the patient was discharged. After discharge, from approximately 20-JAN-2003, the patient had moderate anorexia, nausea and vomiting. At first the patient's clinical sequence was followed at home as she refused to visit the hospital. On _____, the patient was admitted to the hospital for treatment of her anorexia and vomiting. On 21-FEB-2003, she was started on therapy with famotidine, 10 mg daily, for the treatment of gastritis. Concomitant therapy included ginger (+) ginseng (+) maltose (+) zanthoxylum fruit (DAIKENCHUTO), senna (ALOSENN), dextrose (+) electrolytes (unspecified) (+) sodium lactate (SOLITA T-3), dextrose (+) sodium chloride (+) sodium lactate (SOLITA T-1), electrolytes (unspecified) ("VEEN"), gabexate mesylate (FOY) and dextrose. On _____, she developed pancytopenia as revealed by blood sampling [white blood cell count 2030 /mm³, blood platelet count 7.1 x 10⁴/mm³, red blood cell count 256 x 10⁴/mm³. On _____, the pancytopenia worsened as revealed by blood sampling [blood lymphocyte count 44.0 %, blood platelet count 6.8 x 10⁴/mm³, white blood cell count 1860 /mm³, red blood cell count 247 x 10⁴/mm³, blood segmented neutrophil count 41.0%, blood neutrophil count 818 /UL]. On 26-FEB-2003, therapy with famotidine was discontinued. On _____, a bone marrow test was performed and reviewed by the physician. It was considered that the drug-induced hypoplasia of the bone marrow and pancytopenia was related to therapy with famotidine which was administered after admission. On _____, the pancytopenia advanced [blood lymphocyte count 41.7 %, blood platelet count 2.2 x 10⁴/mm³, white blood cell count 1920 /mm³, red blood cell count 183 x 10⁴/mm³, blood segmented neutrophil count 55.4]. On _____, the patient's general condition worsened and the patient died at 12:33 P.M. Bone marrow test was done on _____. Drug-induced pancytopenia due to Daiken-Chuto or famotidine was suspected. The physician reported that therapy with famotidine was more likely to be "responsible". The cause of death was pancytopenia. The Report on Myelogram Classification noted: Normocellular

marrow. From the Report on Myelogram Classification, blood dyscrasia such as acute leukemia, myelodysplastic syndrome and aplastic anemia are ruled out. From this myelogram, metastasis of cancer was unlikely. Because there are many relatively young cells in both myeloid and erythroid, it seems possible that the patient was in a recovery stage from myelosuppression due to some reason or other (famotidine?). No metastatic tumor was observed. Dysplasia was unclear.

Comment: The pancytopenia may have been drug induced with famotidine being a possible cause. There were multiple dietary supplements that confound the case.

E. WAES reports retrieved for QT prolongation

WAES 93071004—20 year old suicide attempt who ingested nortriptyline and famotidine. Patient had sinus tachycardia and QT prolongation on EKG.

Comment: This case (also included under deaths) is consistent with nortriptyline overdose.

WAES 98061788 VENTRICULAR TACHYCARDIA; BRADYCARDIA NOS; DIZZINESS POSTURAL; ELECTROCARDIOGRAM QT PROLONGED; HYPONATRAEMIA; PITUITARY TUMOUR BENIGN NOS (Japan). A 69 year old male with a 5-6 pack/day habit of smoking, pituitary neoplasm, mitral valve stenosis, mitral valve regurgitation and a history of gastrointestinal ulcer, appendectomy and alcoholism who was placed on therapy with famotidine, tablet, 40 mg daily for the treatment of infectious gastroenteritis (duration unknown). Concomitant therapy included cetraxate HCL, "Toughmac E", lactic acid, magaldrate and "Biosin". On _____ the patient was hospitalized for acute gastritis. The patient was placed on liquid replacement therapy and fasting. On 26-APR-1998 the patient experienced prolonged QT interval with bradycardia and dizziness on standing (QTc unknown). Initial serum sodium results were 115 on _____. The sodium results on _____ were 116. On _____ the serum sodium went up to 136. Also on _____ a head computed axial tomography and head magnetic resonance imaging were performed. A pituitary tumor was suspected. On 09-MAY-1998 the patient developed ventricular tachycardia (torsade de pointes), which resolved without intervention. The subsequent rhythm was sinus bradycardia. The patient's condition was managed with MgSo4 and lidocaine injection. Dobutamine HCL continuous infusion was also started. There were two further episodes of ventricular tachycardia while the patient was sleeping. Subsequently there were no further episodes of ventricular tachycardia. The patient then underwent a cardiac catheterization on _____. No significant stenosis of the coronary artery was seen. Mitral stenosis was noted. The patient was then transferred to another hospital on _____. Follow up examination was performed there. The patient was found to be in sinus bradycardia with prolonged QT intervals present. The patient was also found to have conjunctiva less anemic, anterior systolic murmur detected by auscultation, and pulmonary and abdominal findings were normal. There was also no lower extremity peripheral edema noted. Reflexes were normal. There was no further ventricular tachycardia. On 18-MAY-1998 therapy with famotidine was discontinued and patient was started on roxatidine acetate HCL. Subsequently the patient experienced some QT reduction. The reporting physician felt that the patient's experience was related to treatment with famotidine.

QTc ————— 0.50 sec
 ————— 0.47 sec
 ————— 0.46 sec

Comment: This patient was on concomitant medications and had comorbid conditions. The patient was an alcoholic who was placed on therapy with famotidine for an infectious gastroenteritis. These factors could have caused electrolyte abnormalities such as hypomagnesemia or hypokalemia which could have affected the QT interval and contributed to an arrhythmia. The patient was also suspected to have a central pituitary lesion which also could have affected the QT interval.

WAES 95020858 (Japan) ELECTROCARDIOGRAM QT PROLONGED; TORSADE DE POINTES; VENTRICULAR FIBRILLATION. A physician reported that a 66-year-old female patient with idiopathic pulmonary fibrosis, heart failure, pulmonary hypertension, hypertension accompanied by cystic disease of the kidney and a colon polyp, urolithiasis, goiter, and shingles, was placed on therapy with famotidine 10 mg daily on 06FEB90. Concomitant medications included naproxen, bromhexine HCl, codeine phosphate, mixture of digestants (MM Powder), ipriflavone, procaterol HCl (Meptin), ethyl icosapentate, benproperine phosphate, azosemide, and ubidecarenone. Concomitant therapy with nilvadipine was discontinued on 16AUG94. In follow-up the physician reported that in approximately June 1994 the patient developed dyspnea "whenever her body moved" and edema in her lower leg. She was treated with diuretics for right cardiac failure due to pulmonary hypertension, and the edema resolved and dyspnea was relieved. On 01JAN95 the patient developed a cough, cyanosis and fatigue. Therapy with all medications was discontinued on 02JAN95. On 03JAN95 the patient's dyspnea worsened and she lost consciousness. An ECG on _____ revealed an extension of QT (0.66), and torsades de pointes was confirmed. Torsades de pointes spontaneously resolved the same day but changed to ventricular fibrillation on the same day. She was given direct defibrillation and recovered. On _____ the patient was hospitalized for her experiences. Therapy with famotidine, and "all suspended drugs" was reinitiated on 12JAN95. On _____ QT was 0.67 (prior QT upon admission was 0.60), and therapy with famotidine was discontinued. On _____ QT was 0.76, and torsades de pointes recurred. The remaining medications were discontinued. The patient was treated with oral and IV magnesium. On _____ an extracorporeal pacemaker was implanted, and QT recovered to almost previous levels (0.68 on _____ and 0.54 on _____). The patient was treated with IV famotidine (dosage not reported) on 25JAN95, and although no ventricular fibrillation developed, an extended period of monophasic action potential was confirmed. The physician stated that "although a causal relationship with famotidine was suspected, the drugs were administered over a long period and the effects of combined drugs has yet to be clarified. In particular, marked QT extension was recognized even after the suspected drug was discontinued". The physician suspected a causal relationship between the patient's experience and therapy with famotidine because: QT extension due to the suspected drug was experienced, ventricular fibrillation due to famotidine and QT extension were reported, recurrence of ventricular fibrillation after resumption of drug therapies, and marked QT extension following administration of IV famotidine. No further details were provided.

Comment: The reporting physician suspected a causal relationship with famotidine and the events. After IV famotidine was given, an extended period of monophasic action potential was confirmed, although no ventricular fibrillation developed. However, QT remained prolonged and

Torsades was reported 3 days after famotidine was discontinued, while the patient was still on her other medications. Micromedix reports "that EKG changes (ST-SEGMENT DEPRESSION, SINUS TACHYCARDIA and QT-PROLONGATION) occurred in several children receiving procaterol tablets and syrup (Kemp et al, 1985). EKG changes were not considered clinically significant." The patient had been on these medications for years, and over the previous several months she had been placed on a diuretic, which may have caused electrolyte abnormalities that could also have contributed to these events.

WAES 96120346-- ELECTROCARDIOGRAM QT PROLONGED 58 year old female with a gastric ulcer and a history of mitral valve replacement because of rheumatic mitral stenosis who was placed on therapy with famotidine, tab, 20 mg, daily. Concomitant therapy included verapamil hydrochloride, tab, 40 mg, three times a day. Other concomitant therapy included nitrazepam, aspirin-dialuminate, spironolactone, furosemide and warfarin potassium. On _____, the patient fainted and was brought to the hospital by ambulance. Fainting fits recurred after admission and torsade de pointes (Tdp) was electrocardiographically monitored. Tdp disappeared in less than one minute. While no fits recurred, QT prolongation (QT time: 0.52 sec, QT: 0.49), ventricular extrasystole interpolated sinus bradycardia (HR: 40 bpm) were seen. Her serum potassium level was high on admission (5.6 mEq/l). Therapy with verapamil hydrochloride was discontinued on 06JUN96, therapy with famotidine was continuously given. Her hyperkalemia was corrected. Bradycardia was treated with "Alotec" and mexiletine HCL (Mexitil), while an external cardiac pacemaker was used to cope with the symptom. No fits recurred after insertion or removal. Subsequently, the patient recovered. The physician commented that "QT prolonged syndrome was presumably caused by a concurrence of rheumatic myocardopathy, verapamil hydrochloride and hyperkalemia, but it could not be confirmed, as many respects have yet to be clarified".

Comment: These events should not be attributed to famotidine since the symptoms recovered while on the patient continued on famotidine.

WAES 99050386 ELECTROCARDIOGRAM QT PROLONGED; HEPATIC CIRRHOSIS NOS; OEDEMA NOS; OLIGURIA; WEIGHT INCREASED. A 48 year old male physician reported that he developed cirrhosis, oliguria, edema, weight gain and a prolonged QT interval and was hospitalized while on therapy with famotidine. The physician with hypokalemia, hypoproteinemia, NSAID allergy, cirrhosis and a history of lower back pain, ascites, endoscopy, edema, pruritis, abdominal pain, gastric erosion, cholelithiasis and a laparoscopic cholecystectomy was started on therapy with famotidine 40 mg daily, on 22-APR-1988, for the treatment of epigastric pain and a suspected gastric ulcer. Concomitant therapy included amino acids, potassium chloride, furosemide, spironolactone and canrenone free potassium salt. In _____ the patient was hospitalized for decompensated cirrhosis and a electrocardiogram performed revealed flat inverted T-waves in leads II and AVF, but a normal QTc of 0.44 seconds. The patient's serum potassium level and the albumin-corrected serum calcium level were recorded as normal. Therapy with famotidine was discontinued in approximately July, 1998. The physician was discharged from the hospital on approximately _____. In October 1998 therapy with famotidine, 40 mg daily, was restarted for the treatment of epigastric pain. On approximately 05-APR-1999 the physician developed oliguria, edema and weight gain. Subsequently on (_____) the physician was admitted to the hospital for worsening of oliguria, edema and weight gain. A electrocardiogram performed a QT abnormality with a QTc of 0.48, with wide-based, notched T-waves and one isolated premature ventricular contraction.

The physician's serum potassium was 3.9 mg/dl and in conflicting information the patient's serum potassium was reported as 4.1 mEq/L. The patient also has a serum magnesium level of 2.0 mg/dl and a serum albumin corrected serum calcium level of 10.4 mEq/L. Therapy with famotidine furosemide and spironolactone were discontinued on 10-APR-1999, but conflicting information reported that the patient continued therapy with furosemide and spironolactone had continued. The physician's "electrolyte levels were normal". On _____ electrocardiography performed revealed a QT of 0.43 and a QTc of 0.44. At the time of this report the patient's electrocardiogram had remained normal.

Comment: This case was published as a letter to the editor in the American Journal of Medicine 2000; 108:438-9, by Takao Endo "Famotidine and Acquired Long QT syndrome". This report described an asymptomatic long QT interval that normalized after discontinuation of famotidine 40 mg daily, in a 48 year old Japanese man with a history of cirrhosis. This person had also been on diuretics but had normal potassium, magnesium, and calcium levels.

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