TITLE******** **/***/****

Requested by:**ID*

PL No:****PLNO**********

Holder:***HOLDER**********

Formulation No:***FORMNO

Licensed name(s): **MORE**

LN1********

LN2********

LN3********

LN4********

LN5********

CPS/ CSM paper
followed by Medicines Commission paper

NOT FOR PUBLICATION

RESTRICTED-COMMERCIAL	**NUMBER: PL 0025/0312 and 0313**
VARIATION APPLICATION REQUESTING GSL LEGAL STATUS	**PRODUCT NAME:** Pepcid AC Tablets and Pepcid AC Chewable Tablets
LICENCE HOLDER: Merck Sharp and Dohme Ltd Hertford Road Hoddesdon Hertfordshire EN11 9BU	**THERAPEUTIC CLASSIFICATION:** **H_2 receptor antagonist** **RECEIVED:** November 1999 **MEETING:** 2 March 2000
ACTIVE INGREDIENT Famotidine	**CHEMISTRY PHARMACY AND STANDARDS**
LEGAL STATUS: P to GSL	**CONSIDERATION BY OTHER COMMITTEES:** CSM
SALE/SUPPLY General Sales Outlets	**ASSESSORS:** **Pharmaceutical:** [redacted] **Scientific:** **Medical:**

Summary: Variation application requesting a change of legal status from P to GSL for famotidine in the treatment of short-term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity

	Page
Index	1
Introduction	
Background	
Legal Classification of Related Substances	
Assessment	
Product Information	
Conclusion	
Index of Attachments	

APPLICATION FOR A NATIONAL VARIATION TO A MARKETING AUTHORISATION FOR ADDITIONAL STATUS AS A GSL PRODUCT FOR PEPCID AC TABLETS AND PEPCID AC CHEWABLE TABLETS

LICENCE No:	00025/0312 and /0313
PROPRIETARY NAME:	Pepcid AC Tablets and Pepcid AC Chewable Tablets
ACTIVE CONSTITUENTS:	Famotidine
COMPANY NAME:	Merck Sharp and Dohme Ltd
LEGAL STATUS:	P to GSL

1. INTRODUCTION AND BACKGROUND

This application seeks approval to change the current legal status of Pepcid AC Tablets and of Pepcid AC Chewable Tablets (both formulations containing l0mg famotidine) from Pharmacy to General Sale List (Annex 1).

Famotidine is a potent histamine H_2-receptor antagonist which was first registered in the United Kingdom in 1987 for the treatment of gastric and duodenal ulcers and other acid-related conditions.

In 1994 the legal status was changed to Pharmacy for two different formulations of 10mg tablets, developed for the purpose: Pepcid AC Tablets and Pepcid AC Chewable Tablets. The indications granted were short term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity and the prevention of these symptoms when associated with food and beverage, including nocturnal symptoms associated with the evening meal and expected to cause sleep disturbance. The recommended dosage was 1 tablet up to a maximum daily dosage of 2 tablets (20mg), and the maximum duration of treatment was 14 days. (Annex 2)

The company proposes that for General Sale List status the indications, and the pack size should be restricted as follows: -

- *Short-term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity.*
- *Pack-size to be limited to 2, 6, 10 and 12 tablets for Pepcid AC Tablets*
- *Pack-size to be limited to 2,6, 8, 10 and 12 tablets for Pepcid AC Chewable Tablets (Annex 3).*

The company proposes to maintain the duration of treatment as 14 days, and the patient groups remain as for the P product as do the contraindications:

Hypersensitivity to any component of this product and, unless advised by their physician:

- Patients with moderate or severe renal failure
- Patients with severe hepatic impairment

- Patients suffering from any other illness or taking any medications either physician-prescribed or self-prescribed.
- Patients who are middle aged or older with new or recently changed dyspeptic symptoms.
- Patients with unintended weight loss in association with dyspeptic symptoms.

In addition patients must seek medical advice if

- Symptoms fail to respond
- Symptoms recur following self-treatment with Pepcid AC
- If symptoms persist after two weeks treatment)
- If they have difficulty swallowing, or abdominal discomfort persists (Annex 2).

As Pepcid AC and Pepcid AC Chewable already have Marketing Authorisations as Pharmacy medicines, and the formulations and pharmacological and toxicological data are identical, there are no quality or efficacy issues to address, subject to review of the proposed SPC (Annex 3) and product information (Annex 4). The main criterion to consider is the safety in the unsupervised use as a GSL medicine.

2. LEGAL RECLASSIFICATION OF RELATED SUBSTANCES

All authorised H_2-receptor antagonists in the UK, including famotidine, are on the POM Order with exemptions for pharmacy supply for symptomatic treatment and prevention of heartburn and other acid-related symptomatology for a maximum of 14 days.

In September 1999 ranitidine, as *Zantac 75 Relief*, was the first H_2-receptor antagonist to be granted General Sale List status for symptomatic relief only (of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity), restricted to a maximum of 6 days duration. Thus, this application for famotidine will be the second application in the UK for GSL availability of an H_2-receptor-antagonist drug.

The only other therapy available GSL for the management of acid-related symptoms are antacids and alginates, which have been widely used for many years.

3. CRITERION FOR GSL STATUS

Section 51 of The Medicines Act 1968 states, GSL may be appropriate for medicines which can with reasonable safety be sold or supplied otherwise than by or under the supervision of a pharmacist

The term 'with reasonable safety' has been defined as: where the hazard to health, the risk of misuse, or the need to take special precautions in handling is small and where wider sale would be a convenience to the purchaser'.

The company has addressed the criteria in a clinical expert statement, written by [redacted] R & D Johnson & Johnson MSD Europe) together with a report on supporting data (Annex

1). As there are no special precautions in handling this product, this aspect does not need further consideration.

Similarly, considering convenience to the purchaser, although there is an increased availability of retail pharmacies out of normal working hours, not all members of the public have easy access to them.

4. ASSESSMENT

4.1 Hazard To Health

4.1.1 Safety of famotidine as a prescription product

Famotidine (20mg and 40 mg) was first registered in 1984 and has been used extensively world-wide, being licensed in 81 countries.

In clinical trials, the overall incidence for adverse drug reactions was 5% for famotidine, similar to that for ranitidine or placebo.

In the period January 1995 – July 1999, 3,567 million tablets were prescribed, which the company estimates to represent 30 million patients. The company have submitted a Periodic Safety Update Report supplement covering the period January 1995 – August 1999, which was consistent with previous data and showed that 20 mg and 40 mg famotidine continued to be generally well-tolerated.

Assessors comment
The pattern observed was similar to that in the UK drug analysis print for famotidine (Annex 5). (578 reactions in 372 reports, one of which was fatal (pulmonary embolism). The number of tablets sold in the UK over this period (1987 to date) was *XXXXX*. (Awaiting response from company).

Famotidine has a very similar safety profile compared to ranitidine, which has recently received GSL status for its 75 mg tablets (UK drug analysis print - Annex 6). Unlike cimetidine, neither drug alters plasma hormone levels, binds to androgen receptors, nor inhibits the mixed function oxidases (and therefore do not share the same potential to interact with other drugs by this mechanism).

4.1.2 Safety of famotidine as an OTC product

The 10 mg tablets were developed for use as OTC products, and have been registered as such in 15 countries since 1994. Over the period 1994- 1997, approximately 115 million packs have been sold equating, the company estimates, to 50 million patients. A summary table covering the period January 1995 – August 1999 has been provided (Annex 7). In this period there were 10,579 events reported in 9584 episodes. The most commonly reported adverse drug reactions were Lack of response; diarrhoea; constipation; headache; nausea; dizziness; rash; dry mouth; pruritis; abdominal pain; insomnia; somnolence and vomiting. The pattern observed was again similar to that in the UK drug analysis print. Only 132 of these spontaneous reports were classified as serious.

Assessors comment
The most commonly reported adverse drug reactions are already reflected in the SPC for the P product apart from insomnia and somnolence. The other reported reactions are not included in the SPC for P product and it is not considered necessary to add them for the GSL product.

Most of the serious reactions reported were single reports. Although 10 of the serious reactions (21 events) were of potential concern their occurrence must be put in context against a background of well over 115 million patient packs sold in 1994 – 1997 alone.

4.2 RISK OF MISUSE/INAPPROPRIATE USE

4.2.1. Potential for abuse

There is no evidence that famotidine has any significant potential for abuse and clinical trials have not revealed any association between famotidine and euphoria. The applicant claims that, like ranitidine, famotidine has a large margin of safety in overdose and no serious effects directly attributable to the drugs have been recorded when overdose has occurred (Annex 1).

4.2.2 Lack of professional supervision

It is important that the ability to self-medicate without the supervision of a pharmacist does not lead to the delay in diagnosis of serious, underlying diseases for which other or additional therapy is more appropriate, especially those such as gastric or gastro-oesophageal cancer where the earliest possible diagnosis is desirable.

It is claimed that approximately 1 in 3 apparently healthy people in Britain experience heartburn but only 1 in 10 suffer more than once a week (Annex 1). Of 40% of the population who experienced dyspepsia in a six month period, only one quarter (i.e. 10% of the population) consulted their GP, the rest opting for self-care (Annex 8). The symptoms of heartburn and acid reflux are the most easily described and recognised symptoms for patients, who are often able to identify particular food or drinks that trigger them (Annex 1). They have had access to antacids for self medication for many years.

Assessors comment
The use of famotidine can be regarded as only part of the overall management of the symptoms which should include attention to diet (possibly reductions in alcohol intake), weight loss and general improvement in a healthy life style (Annex 8). The company should consider including educational information in the leaflet regarding life-style changes to improve their symptoms.

4.2.2.1 Underlying disease

The applicant has put forward an argument that, despite self-medication, the underlying conditions remain relatively unchanged and, since H_2-antagonists for the current attack do not reduce the overall heartburn rate per week, these patients with recurrent symptoms would be likely to seek medical advice (Annex 9).

For more serious conditions the low doses of H_2-antagonist would only provide partial and short-term relief, and patients are likely to seek medical advice in this situation. This is supported by warnings in the patient information which advise patients to consult their doctor if symptoms persist.

Regarding malignancy, the company note that it is uncommon for patients to present with heartburn alone (4%), in the absence of weight loss, dysphagia and anaemia. The product information contra-indicates patients with unintended weight loss in association with dyspeptic symptoms. They also comment that gastric cancer develops over a long period of time, e.g. in the early stages this may be as much as 1½-10 years for a tumour to double in size and cite references where there appears to be no correlation between delay in diagnosis and the stage of disease (Annex 1). Nevertheless they agree that early self-referral should be the aim.

In addition the company cites studies in the UK, Sweden & USA which show that the number of prescriptions written for the H_2-receptor antagonists has not been affected by the introduction of OTC packs, and that in Sweden and America the tendency to consult a doctor was not affected either (Annex 1).

Assessor Comments
The proposed leaflet highlights the warning signs which might identify those patients requiring investigation due to underlying disease and this is appropriate. However the SPC should be amended to include a warning such as "Treatment with a histamine H_2 antagonist may mask symptoms associated with carcinoma of the stomach and may therefore delay diagnosis of the condition".

Neither the proposed SPC nor the leaflet and labelling carries a warning for users of NSAIDs who also constitute an at risk group, especially the elderly. It is recommended that a warning such as "Patients who are taking non-steroidal anti-inflammatory drugs, especially the elderly, should consult their doctor before taking this product." be included in the SPC and consequently in the patient information.

4.2.3 Dosage

The company have supplied literature comparing the effect of several doses, but predominately 10 mg, of famotidine with that of 75mg ranitidine on various elements of acid secretion, and also efficacy of the two drugs on heartburn. Famotidine is more potent than ranitidine, many papers quoting the differential as seven times more potent.

Assessor Comment
On the evidence presented to us the proposed dosage of 10mg has been supported by both pharmacodynamic and efficacy studies.

4.2.4 Duration of Use

The company has proposed 14 days of self-medication before seeking medical advice, as approved for the P product.

Assessor Comment

In light of the concerns raised above (Section 4.2.2.1), it is suggested that for the GSL product the maximum duration should be six days. Accordingly the posology for the GSL products should be amended from "The maximum treatment is two weeks" to read "Do not take for more than 6 days or purchase a second pack of tablets without the advice of a pharmacist or doctor".

Thus, a pack of 12 tablets would conveniently provide 6 days treatment at the maximal daily dose.

5. PRODUCT INFORMATION

5.1 Summary of Product Characteristics

5.1.1 Name of Medicinal Product

The company has not proposed separate names for the GSL presentation of the products, even though the indications will not be the same. A separate name to distinguish the GSL pack from the P pack should be proposed for each product.

5.1.2 Posology and Method of Administration

"The maximum treatment is two weeks" should be amended to read "Do not take for more than 6 days or purchase a second pack of tablets without the advice of a pharmacist or doctor".

5.1.3 Special warnings and precautions

The following warnings and precautions should be added:

i) Treatment with a histamine H_2- receptor antagonist may mask symptoms associated with carcinoma of the stomach, and may therefore delay diagnosis of the condition.

ii) Patients who are taking non-steroidal anti-inflammatory drugs, especially the elderly should consult their doctor before taking this product".

Reference to these warnings and precautions should also be required to be included in the patient information leaflet and labelling.

5.2 Patient Information Leaflets (Annex 4).

These should be amended to be consistent with the Summary of Product Characteristics, and in addition:

i) The contra-indications should be more firmly expressed. e.g. "Do not take without seeking the advice of your doctor or pharmacist". The special warnings and precautions may be included under this heading.

ii) Both leaflets should refer to pregnancy and lactation.

iii) It is not acceptable to include statements such as "….has not been shown to interact with other medicines" or "…..or alcohol". These should be deleted.

iv) References to clinical trials should be removed.

v) Suitable information on life-style changes to improve the symptoms should be included in the leaflet.

5.3 Labelling/Carton Text (Annex 4)

These should be amended to be consistent with the SPC, and in addition:

i) Reference to the contraindications should be included on the carton.

ii) Reference to the special warnings and precautions should be included on the carton.

iii) Selective use of indications on the front of the carton is not acceptable.

iv) Promotional statements are not acceptable.

6. ASSESSORS' CONCLUSIONS

This application seeks approval to change the current legal status of Pepcid AC Tablets and of Pepcid AC Chewable Tablets from Pharmacy to General Sale List for short-term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity. It will be the second application in the UK for GSL availability of an H_2-receptor-antagonist drug.

The indications requested for GSL are covered by, but more restrictive than, those already granted to this product for Pharmacy only use. These are most easily described and recognised symptoms for patients and therefore would support the approval of this application.

The expert statement, together with a report on supporting data, has addressed the criterion for GSL status, including the risk of inappropriate use occasioned by the lack of supervision by a pharmacist. The applicant considers that patients with underlying disease will experience relapses (whether taking the drug or not at the time depending on the nature of the disease), and the recurrence of their symptoms would prompt them to seek medical advice. Nevertheless, the assessors consider that the maximum duration for self-medication should be reduced from 14 days to 6 days.

In the main, the evidence presented by the applicant is reassuring that the lack of supervision by a pharmacist will not have a detrimental effect on the patient. However, it is felt that in two particular cases of underlying disease, the application would be strengthened by the addition of special warnings and precautions in the SPC. These would refer to the risk of gastric carcinoma and the risk to NSAID users, together with reference to the latter warning on the patient information.

The safety profile of famotidine is acceptable and the provision of a database dedicated to non-prescription use has not revealed any unexpected data, despite sales of over 115 million packs world-wide.

It may be concluded that this application for availability by GSL is supported by the evidence presented.

7. RECOMMENDATIONS

The Committee is asked to consider whether famotidine may safely be supplied otherwise than by or under the supervision of a pharmacist for short-term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity, at a dosage of 10 mg (20 mg maximum daily dose) and with a pack size of up to 12 tablets.

The Medicines (Products Other than Veterinary Drugs) (General Sales List Order) 1984 and the Medicines (Sale and Supply) (Miscellaneous Provisions) Regulations 1980 should be amended accordingly to allow sale and supply as a General Sales List product.

[redacted]

February 2000

RESTRICTED-COMMERCIAL

NOT FOR PUBLICATION

CPS 2000/ CSM

CPS COMMITTEE	:	**DRAFT ADVICE**
DATE OF MEETING	:	**2 March 2000**
M.A. No	:	**PL 00025/0312 and 0313**
COMPANY	:	**Merck Sharp and Dohme Ltd**
PRODUCT	:	**Pepcid AC Tablets & Pepcid AC Chewable**
	:	**Tablets**
ACTIVE CONSTITUENT	:	**Famotidine**
LEGAL STATUS	:	**P to GSL**
KEY WORDS		

APPLICATION FOR A NATIONAL VARIATION TO A MARKETING AUTHORISATION FOR ADDITIONAL STATUS AS A GSL PRODUCT FOR PEPCID AC TABLETS AND PEPCID AC CHEWABLE TABLETS

LEGAL CLASSIFICATION

The Committee considered whether Pepcid AC Tablets and Pepcid AC Chewable Tablets fall within a description or class specified for the purpose of Section 51 of the Medicines Act 1968 by Order made under Section 51 (1), as being appropriate for supply with reasonable safety, otherwise than by, or under the supervision of, a pharmacist and advised that the GSL Order be amended to allow general sale supply.

The Committee also advised that:-

i. An entry should be made for famotidine in the Medicines (Products Other than Veterinary Drugs) (General Sales List Order) 1984 to allow general sale up to a maximum dose of 10mg and a maximum daily dose up to 20mg.

ii. An entry should be made for famotidine in the medicines (Sale and Supply) (Miscellaneous Provisions) Regulations 1980 to allow up to 12 x 10mg tablets of famotidine to be sold otherwise than at a registered pharmacy.

PRODUCT INFORMATION

The Committee advised that the variation should be granted on condition that the product particulars are amended and in particular:-

1. Summary of Product Characteristics

1.1 Name of Medicinal Product

An alternative product name should be proposed.

1.2 Posology and Method of Administration

The maximum treatment duration is amended to read "Do not take for more than 6 days or purchase a second pack of tablets without the advice of a pharmacist or doctor".

1.3 Special Warnings and Precautions

The following should be added:

i) Treatment with a histamine H_2-receptor antagonist may mask symptoms associated with carcinoma of the stomach, and may therefore delay diagnosis of the condition.

ii) Patients who are taking non-steroidal anti-inflammatory drugs, especially the elderly, should consult their doctor before taking this product.

2. Patient Information Leaflet/Labelling

The patient information leaflets and the labelling should be amended to be consistent with the SPC and to the satisfaction of the Secretariat. Reference to the contra-indications and special warnings and precautions should be included on the outer carton. Promotional statements should be removed from the carton. Suitable information on life-style changes to improve the symptoms should be included in the leaflet.

INDEX OF ATTACHMENTS

MEDICINES COMMISSION

RESTRICTED – COMMERCIAL

AMENDMENT OF THE GSL ORDER – ADDITION OF FAMOTIDINE TO THE MEDICINES (PRODUCTS OTHER THAN VETERINARY DRUGS) (GENERAL SALE LIST) ORDER 1984 TO ALLOW GENERAL SALE UP TO A MAXIMUM DOSE OF 10 MG (MAXIMUM DAILY DOSE 20 MG)

Applicant: **Merck Sharp and Dohme Ltd**
CSM consideration: March 2000
Consultation: **May - June 2000**
Assessors: [redacted]

1. INTRODUCTION

This paper seeks the advice of Medicines Commission on a proposal to add famotidine (up to a maximum dose of 10 mg; maximum daily dose 20 mg; maximum pack size 12 tablets) to the GSL order following CSM advice and public consultation. The proposal follows an application from Merck Sharp and Dohme Ltd requesting GSL status for Pepcid AC tablets 10 mg and Pepcid AC Chewable tablets 10 mg. The CSM paper is attached at Annex MC1, and consultation responses at Annex MC2.

2. BACKGROUND AND LICENSING HISTORY

Famotidine is a potent histamine H_2-receptor antagonist which was first authorised in the United Kingdom in 1987 for the treatment of gastric and duodenal ulcers and other acid-related conditions. In 1994 the POM Order was amended to allow Pharmacy availability for famotidine 10mg tablets for the following indications:

> Short-term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity and the prevention of these symptoms when associated with food and beverage, including nocturnal symptoms associated with the evening meal and expected to cause sleep disturbance.

The recommended dosage was 1 tablet up to a maximum daily dosage of 20mg, and the maximum duration of treatment was 14 days.

The applicant holds two Marketing Authorisations with Pharmacy status for Pepcid AC Tablets and Pepcid AC Chewable Tablets. The request for GSL status proposes the same dose and maximum daily dose as the P products, but limits the indications to treatment of symptoms only i.e. *short-term symptomatic relief of heartburn, indigestion, acid indigestion and hyperacidity*, and the duration of use to 6 days.

The CSM advised in March 2000 that famotidine may be sold or supplied with reasonable safety without the need for pharmacist's supervision. They also recommended that the product

information for Pepcid AC Tablets and Pepcid AC Chewable Tablets should be amended as outlined in the CSM paper (Annex MC1).

3. CONSULTATION

The Consultation letter MLX 262, including this proposal, was issued on 12 May 2000 with a deadline for comments by 22 June 2000.

Specific comments concerning famotidine were received from [redacted] and from the [redacted] and copies of their responses are attached at Annex MC2.

4. DISCUSSION

The response from the [redacted] was favourable as they consider that famotidine "is a perfectly safe and acceptable H_2 receptor antagonist".
As the comments from [redacted] and from the [redacted] are similar, they can be addressed together. Both organisations consider that: -

1) Histamine H_2-receptor antagonist are not suitable for long-term use or repeated use without monitoring. When used in self-medication for symptomatic relief of indigestion they can mask the symptoms of early gastric cancers, especially in the over 40s. Although the pack size has been restricted this does not prevent the purchase of several packs together or of regular purchase of packs.

2) The lack of appropriate advice which would have been given by pharmacy-trained staff is of concern.

The principle of GSL availability for H_2-receptor antagonists has already been established with the reclassification of ranitidine for GSL availability in September 1999. The concerns regarding wider availability of this category have therefore been addressed.

The other concerns have already been considered by CSM, and amendments to the product information have been sought. In particular, the maximum treatment duration was specifically amended to "Do not take for more than 6 days *or purchase a second pack of tablets without the advice of a pharmacist or doctor*". This draws attention to the need for medical advice should symptoms persist to avoid casual repeat purchase of famotidine by the consumer. In addition, a warning on the masking of cancer must be added to the SPC and expressed in non-alarming terms in the patient information leaflet. Other warnings relating to the signs and symptoms of gastric cancer, especially in the over 45 year-old age-group, are already included in the SPC and will be present on the outer carton of the product. The patient will therefore have access to suitable information on the pack and in the patient information leaflet to ensure safe use of the product without pharmacist supervision. In addition, the company will be asked to add a section on life-style and symptomatic relief.

5. ADVICE SOUGHT

Medicines Commission is requested to advise on whether famotidine (up to a maximum dose of 10 mg; maximum daily dose 20 mg; maximum pack size 12 tablets) can, with reasonable safety, be sold or supplied otherwise than by, or under the supervision of, a pharmacist and therefore whether it should be added to the GSL Order.

[redacted]

June 2000

LIST OF ANNEXES

ANNEX MC1 CSM paper, March 2000

ANNEX MC2 Specific responses to Consultation MLX 262

ANNEX MC1

CSM paper, March 2000

ANNEX MC2

Specific responses to Consultation MLX 262

NOT FOR PUBLICATION

RESTRICTED-COMMERCIAL	**NUMBER: PL 0025/0312 and 0313**
VARIATION APPLICATION REQUESTING GSL LEGAL STATUS	**PRODUCT NAME:** Pepcid AC Tablets and Pepcid AC Chewable Tablets
LICENCE HOLDER: Merck Sharp and Dohme Ltd Hertford Road Hoddesdon Hertfordshire EN11 9BU	**THERAPEUTIC CLASSIFICATION:** **H_2 receptor antagonist** **RECEIVED:** November 1999 **MEETING:** 2 March 2000
ACTIVE INGREDIENT Famotidine	**CHEMISTRY PHARMACY AND STANDARDS**
LEGAL STATUS: P to GSL	**CONSIDERATION BY OTHER COMMITTEES:** CSM
SALE/SUPPLY General Sales Outlets	**ASSESSORS:** **Pharmaceutical:** [redacted] **Scientific:** **Medical:**

Summary: Variation application requesting a change of legal status from P to GSL for famotidine in the treatment of short-term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity

Index	**Page**

APPLICATION FOR A NATIONAL VARIATION TO A MARKETING AUTHORISATION FOR ADDITIONAL STATUS AS A GSL PRODUCT FOR PEPCID AC TABLETS AND PEPCID AC CHEWABLE TABLETS

LICENCE No:	00025/0312 and /0313
PROPRIETARY NAME:	Pepcid AC Tablets and Pepcid AC Chewable Tablets
ACTIVE CONSTITUENTS:	Famotidine
COMPANY NAME:	Merck Sharp and Dohme Ltd
LEGAL STATUS:	P to GSL

1. INTRODUCTION AND BACKGROUND

This application seeks approval to change the current legal status of Pepcid AC Tablets and of Pepcid AC Chewable Tablets (both formulations containing l0mg famotidine) from Pharmacy to General Sale List (Annex 1).

Famotidine is a potent histamine H_2-receptor antagonist which was first registered in the United Kingdom in 1987 for the treatment of gastric and duodenal ulcers and other acid-related conditions.

In 1994 the legal status was changed to Pharmacy for two different formulations of 10mg tablets, developed for the purpose: Pepcid AC Tablets and Pepcid AC Chewable Tablets. The indications granted were short term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity and the prevention of these symptoms when associated with food and beverage, including nocturnal symptoms associated with the evening meal and expected to cause sleep disturbance. The recommended dosage was 1 tablet up to a maximum daily dosage of 2 tablets (20mg), and the maximum duration of treatment was 14 days. (Annex 2)

The company proposes that for General Sale List status the indications, and the pack size should be restricted as follows: -

- *Short-term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity.*
- *Pack-size to be limited to 2, 6, 10 and 12 tablets for Pepcid AC Tablets*
- *Pack-size to be limited to 2,6, 8, 10 and 12 tablets for Pepcid AC Chewable Tablets (Annex 3).*

The company proposes to maintain the duration of treatment as 14 days, and the patient groups remain as for the P product as do the contraindications:

Hypersensitivity to any component of this product and, unless advised by their physician:

- Patients with moderate or severe renal failure
- Patients with severe hepatic impairment

- Patients suffering from any other illness or taking any medications either physician-prescribed or self-prescribed.
- Patients who are middle aged or older with new or recently changed dyspeptic symptoms.
- Patients with unintended weight loss in association with dyspeptic symptoms.

In addition patients must seek medical advice if

- Symptoms fail to respond
- Symptoms recur following self-treatment with Pepcid AC
- If symptoms persist after two weeks treatment)
- If they have difficulty swallowing, or abdominal discomfort persists (Annex 2).

As Pepcid AC and Pepcid AC Chewable already have Marketing Authorisations as Pharmacy medicines, and the formulations and pharmacological and toxicological data are identical, there are no quality or efficacy issues to address, subject to review of the proposed SPC (Annex 3) and product information (Annex 4). The main criterion to consider is the safety in the unsupervised use as a GSL medicine.

2. LEGAL RECLASSIFICATION OF RELATED SUBSTANCES

All authorised H_2-receptor antagonists in the UK, including famotidine, are on the POM Order with exemptions for pharmacy supply for symptomatic treatment and prevention of heartburn and other acid-related symptomatology for a maximum of 14 days.

In September 1999 ranitidine, as *Zantac 75 Relief*, was the first H_2-receptor antagonist to be granted General Sale List status for symptomatic relief only (of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity), restricted to a maximum of 6 days duration. Thus, this application for famotidine will be the second application in the UK for GSL availability of an H_2-receptor-antagonist drug.

The only other therapy available GSL for the management of acid-related symptoms are antacids and alginates, which have been widely used for many years.

3. CRITERION FOR GSL STATUS

Section 51 of The Medicines Act 1968 states, GSL may be appropriate for medicines which can with reasonable safety be sold or supplied otherwise than by or under the supervision of a pharmacist

The term 'with reasonable safety' has been defined as: where the hazard to health, the risk of misuse, or the need to take special precautions in handling is small and where wider sale would be a convenience to the purchaser'.

The company has addressed the criteria in a clinical expert statement, written by [redacted] R & D Johnson & Johnson MSD Europe) together with a report on supporting data (Annex 1).

4. ASSESSMENT

4.1 Hazard To Health

4.1.1 Safety of famotidine as a prescription product

Famotidine (20mg and 40 mg) was first registered in 1984 and has been used extensively world-wide, being licensed in 81 countries.

In clinical trials, the overall incidence for adverse drug reactions was 5% for famotidine, similar to that for ranitidine or placebo.

In the period January 1995 – July 1999, 3,567 million tablets were prescribed, which the company estimates to represent 30 million patients. The company have submitted a Periodic Safety Update Report supplement covering the period January 1995 – August 1999, which was consistent with previous data and showed that 20 mg and 40 mg famotidine continued to be generally well-tolerated.

Assessors comment
The pattern observed was similar to that in the UK drug analysis print for famotidine (1987-date) (Annex 5). (578 reactions in 372 reports, one of which was fatal (pulmonary embolism).

Famotidine has a very similar safety profile compared to ranitidine, which has recently received GSL status for its 75 mg tablets (UK drug analysis print - Annex 6). Unlike cimetidine, neither drug alters plasma hormone levels, binds to androgen receptors, nor inhibits the mixed function oxidases (and therefore do not share the same potential to interact with other drugs by this mechanism).

4.1.2 Safety of famotidine as an OTC product

The 10 mg tablets were developed for use as OTC products, and have been registered as such in 15 countries since 1994. Over the period 1994- 1997, approximately 115 million packs have been sold equating, the company estimates, to 50 million patients. A summary table covering the period January 1995 – August 1999 has been provided (Annex 7). In this period there were 10,579 events reported in 9584 episodes. The most commonly reported adverse drug reactions were Lack of response; diarrhoea; constipation; headache; nausea; dizziness; rash; dry mouth; pruritis; abdominal pain; insomnia; somnolence and vomiting. The pattern observed was again similar to that in the UK drug analysis print. Only 132 of these spontaneous reports were classified as serious.

Assessors comment
The most commonly reported adverse drug reactions are already reflected in the SPC for the P product apart from insomnia and somnolence. The other reported reactions are not included in the SPC for P product and it is not considered necessary to add them for the GSL product.

Most of the serious reactions reported were single reports. Although 10 of the serious reactions (21 events) were of potential concern their occurrence must be put in context against a background of well over 115 million patient packs sold in 1994 – 1997 alone.

4.2 RISK OF MISUSE/INAPPROPRIATE USE

4.2.1. Potential for abuse

There is no evidence that famotidine has any significant potential for abuse and clinical trials have not revealed any association between famotidine and euphoria. The applicant claims that, like ranitidine, famotidine has a large margin of safety in overdose and no serious effects directly attributable to the drugs have been recorded when overdose has occurred (Annex 1).

4.2.2 Lack of professional supervision

It is important that the ability to self-medicate without the supervision of a pharmacist does not lead to the delay in diagnosis of serious, underlying diseases for which other or additional therapy is more appropriate, especially those such as gastric or gastro-oesophageal cancer where the earliest possible diagnosis is desirable.

It is claimed that approximately 1 in 3 apparently healthy people in Britain experience heartburn but only 1 in 10 suffer more than once a week (Annex 1). Of 40% of the population who experienced dyspepsia in a six month period, only one quarter (i.e. 10% of the population) consulted their GP, the rest opting for self-care (Annex 8). The symptoms of heartburn and acid reflux are the most easily described and recognised symptoms for patients, who are often able to identify particular food or drinks that trigger them (Annex 1). They have had access to antacids for self medication for many years.

Assessors comment
The use of famotidine can be regarded as only part of the overall management of the symptoms which should include attention to diet (possibly reductions in alcohol intake), weight loss and general improvement in a healthy life style (Annex 8). The company should consider including educational information in the leaflet regarding life-style changes to improve their symptoms.

4.2.2.1 Underlying disease

The applicant has put forward an argument that, despite self-medication, the underlying conditions remain relatively unchanged and, since H_2-antagonists for the current attack do not reduce the overall heartburn rate per week, these patients with recurrent symptoms would be likely to seek medical advice (Annex 9).

For more serious conditions the low doses of H_2-antagonist would only provide partial and short-term relief, and patients are likely to seek medical advice in this situation. This is supported by warnings in the patient information which advise patients to consult their doctor if symptoms persist.

Regarding malignancy, the company note that it is uncommon for patients to present with heartburn alone (4%), in the absence of weight loss, dysphagia and anaemia. The product information contra-indicates patients with unintended weight loss in

association with dyspeptic symptoms. They also comment that gastric cancer develops over a long period of time, e.g. in the early stages this may be as much as 1½-10 years for a tumour to double in size and cite references where there appears to be no correlation between delay in diagnosis and the stage of disease (Annex 1). Nevertheless they agree that early self-referral should be the aim.

In addition the company cites studies in the UK, Sweden & USA which show that the number of prescriptions written for the H_2-receptor antagonists has not been affected by the introduction of OTC packs, and that in Sweden and America the tendency to consult a doctor was not affected either (Annex 1).

Assessor Comments
The proposed leaflet highlights the warning signs which might identify those patients requiring investigation due to underlying disease and this is appropriate. However the SPC should be amended to include a warning such as "Treatment with a histamine H_2 antagonist may mask symptoms associated with carcinoma of the stomach and may therefore delay diagnosis of the condition".

Neither the proposed SPC nor the leaflet and labelling carries a warning for users of NSAIDs who also constitute an at risk group, especially the elderly. It is recommended that a warning such as "Patients who are taking non-steroidal anti-inflammatory drugs, especially the elderly, should consult their doctor before taking this product." be included in the SPC and consequently in the patient information.

4.2.3 Dosage

The company have supplied literature comparing the effect of several doses, but predominately 10 mg, of famotidine with that of 75mg ranitidine on various elements of acid secretion, and also efficacy of the two drugs on heartburn. Famotidine is more potent than ranitidine, many papers quoting the differential as seven times more potent.

Assessor Comment
On the evidence presented to us the proposed dosage of 10mg has been supported by both pharmacodynamic and efficacy studies.

4.2.4 Duration of Use

The company has proposed 14 days of self-medication before seeking medical advice, as approved for the P product.

Assessor Comment

In light of the concerns raised above (Section 4.2.2.1), it is suggested that for the GSL product the maximum duration should be six days. Accordingly the posology for the GSL products should be amended from "The maximum treatment is two weeks" to read "Do not take for more than 6 days or purchase a second pack of tablets without the advice of a pharmacist or doctor".

Thus, a pack of 12 tablets would conveniently provide 6 days treatment at the maximal daily dose.

5. PRODUCT INFORMATION

5.1 Summary of Product Characteristics

5.1.1 Name of Medicinal Product

The company has not proposed separate names for the GSL presentation of the products, even though the indications will not be the same. A separate name to distinguish the GSL pack from the P pack should be proposed for each product.

5.1.2 Posology and Method of Administration

"The maximum treatment is two weeks" should be amended to read "Do not take for more than 6 days or purchase a second pack of tablets without the advice of a pharmacist or doctor".

5.1.3 Special warnings and precautions

The following warnings and precautions should be added:

i) Treatment with a histamine H_2- receptor antagonist may mask symptoms associated with carcinoma of the stomach, and may therefore delay diagnosis of the condition.

ii) Patients who are taking non-steroidal anti-inflammatory drugs, especially the elderly should consult their doctor before taking this product".

Reference to these warnings and precautions should also be required to be included in the patient information leaflet and labelling.

5.2 Patient Information Leaflets (Annex 4).

These should be amended to be consistent with the Summary of Product Characteristics, and in addition:

i) The contra-indications should be more firmly expressed. e.g. "Do not take without seeking the advice of your doctor or pharmacist". The special warnings and precautions may be included under this heading.

ii) Both leaflets should refer to pregnancy and lactation.

iii) It is not acceptable to include statements such as "....has not been shown to interact with other medicines" or ".....or alcohol". These should be deleted.

iv) References to clinical trials should be removed.

v) Suitable information on life-style changes to improve the symptoms should be included in the leaflet.

5.3 Labelling/Carton Text (Annex 4)

These should be amended to be consistent with the SPC, and in addition:

i) Reference to the contraindications should be included on the carton.

ii) Reference to the special warnings and precautions should be included on the carton.

iii) Selective use of indications on the front of the carton is not acceptable.

iv) Promotional statements are not acceptable.

6. ASSESSORS' CONCLUSIONS

This application seeks approval to change the current legal status of Pepcid AC Tablets and of Pepcid AC Chewable Tablets from Pharmacy to General Sale List for short-term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity. It will be the second application in the UK for GSL availability of an H_2-receptor-antagonist drug.

The indications requested for GSL are covered by, but more restrictive than, those already granted to this product for Pharmacy only use. These are most easily described and recognised symptoms for patients and therefore would support the approval of this application.

The expert statement, together with a report on supporting data, has addressed the criterion for GSL status, including the risk of inappropriate use occasioned by the lack of supervision by a pharmacist. The applicant considers that patients with underlying disease will experience relapses (whether taking the drug or not at the time depending on the nature of the disease), and the recurrence of their symptoms would prompt them to seek medical advice. Nevertheless, the assessors consider that the maximum duration for self-medication should be reduced from 14 days to 6 days.

In the main, the evidence presented by the applicant is reassuring that the lack of supervision by a pharmacist will not have a detrimental effect on the patient. However, it is felt that in two particular cases of underlying disease, the application would be strengthened by the addition of special warnings and precautions in the SPC. These would refer to the risk of gastric carcinoma and the risk to NSAID users, together with reference to the latter warning on the patient information.

The safety profile of famotidine is acceptable and the provision of a database dedicated to non-prescription use has not revealed any unexpected data, despite sales of over 115 million packs world-wide.

It may be concluded that this application for availability by GSL is supported by the evidence presented.

7. RECOMMENDATIONS

The Committee is asked to consider whether famotidine may safely be supplied otherwise than by or under the supervision of a pharmacist for short-term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity, at a dosage of 10 mg (20 mg maximum daily dose) and with a pack size of up to 12 tablets.

The Medicines (Products Other than Veterinary Drugs) (General Sales List Order) 1984 and the Medicines (Sale and Supply) (Miscellaneous Provisions) Regulations 1980 should be amended accordingly to allow sale and supply as a General Sales List product.

[redacted]

February 2000

INDEX OF ATTACHMENTS

Annex 1

ADDENDUM TO THE EXPERT REPORT IN SUPPORT OF
PRODUCT LICENCE VARIATION APPLICATION TO
PEPCID AC TABLETS AND CHEWABLE TABLETS
(PL 0025/0312 AND 0025/0313)
TO CHANGE THE LEGAL STATUS FROM PHARMACY TO
GENERAL SALES LIST

Justification for the removal of famotidine from prescription control was presented in the clinical expert report written by [redacted], which accompanied the 1993 product licence application for Pepcid AC 10 mg tablets for pharmacy use.

The issues relevant to the legal classification of famotidine have been revisited and updated in this application.

When the legal status of famotidine was changed from POM to P in the UK, safety had to be extrapolated from data generated on the prescription product. However, famotidine has been available in the United States since June 1995 with a status equivalent to GSL (that is self-selection in drug stores and other outlets) and has been very successful there with sales of 34 million packs in 1997. Therefore extensive experience with the product used in the circumstances now proposed is available. In addition, there are data from many European countries where famotidine 10mg is available as the equivalent of a P medicine.

The data presented in this application enable the following key questions to be addressed:

- Can oral famotidine 10mg reasonably be sold outside the supervision of a pharmacist?
- Is the hazard to health, the risk of misuse, and the need to take special precaution in handling small enough to allow sale in a wider distribution?
- Would wider sale be a convenience to the purchaser?

The H_2 receptor antagonists have been used extensively over the last two decades and have established themselves not only as effective but also as extremely well tolerated medicines. The safety profile of famotidine, like ranitidine, is exceptionally well documented and compares favourably with other medicines that enjoy GSL status. The switch from POM to P in the UK has not given cause for anxiety, and re-classification elsewhere in Europe (as a 'P' medicine) and in the United States (as the equivalent of GSL status) has proved equally beneficial for the consumer without giving rise to concerns for regulators.

The data now justify a change in legal status from P to GSL since there is appropriately little risk to patients from adverse events or the masking of serious disease; additionally risk in overdosage and the potential for misuse are minimal. The indications proposed are readily recognised by consumers and self-medication for them is commonplace. Famotidine offers the consumer an efficacious treatment for acid-related digestive symptoms at a risk comparable or lower than other medicines already used for the same indications in a GSL setting.

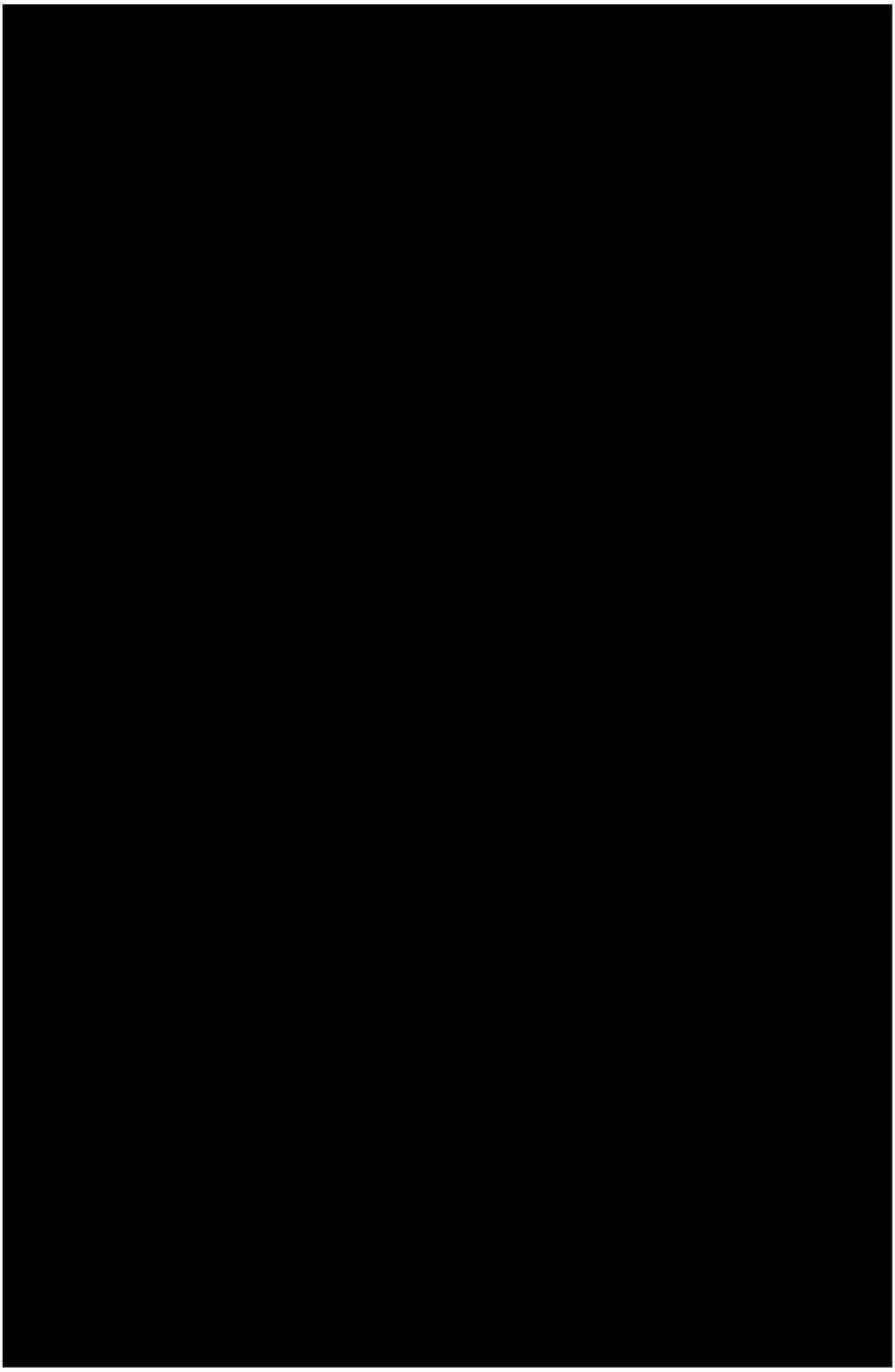
The proposal to limit the maximum pack size for GSL use to 12 tablets is a practical way of limiting the duration of treatment, in common with other medicines available GSL. The value of adhering to an upper limit for unsupervised medication in dyspepsia is recognised and the proposed pack size allows only 6 days treatment at the maximum recommended dose and therefore limits initial therapy to less than half of the generally advised period.

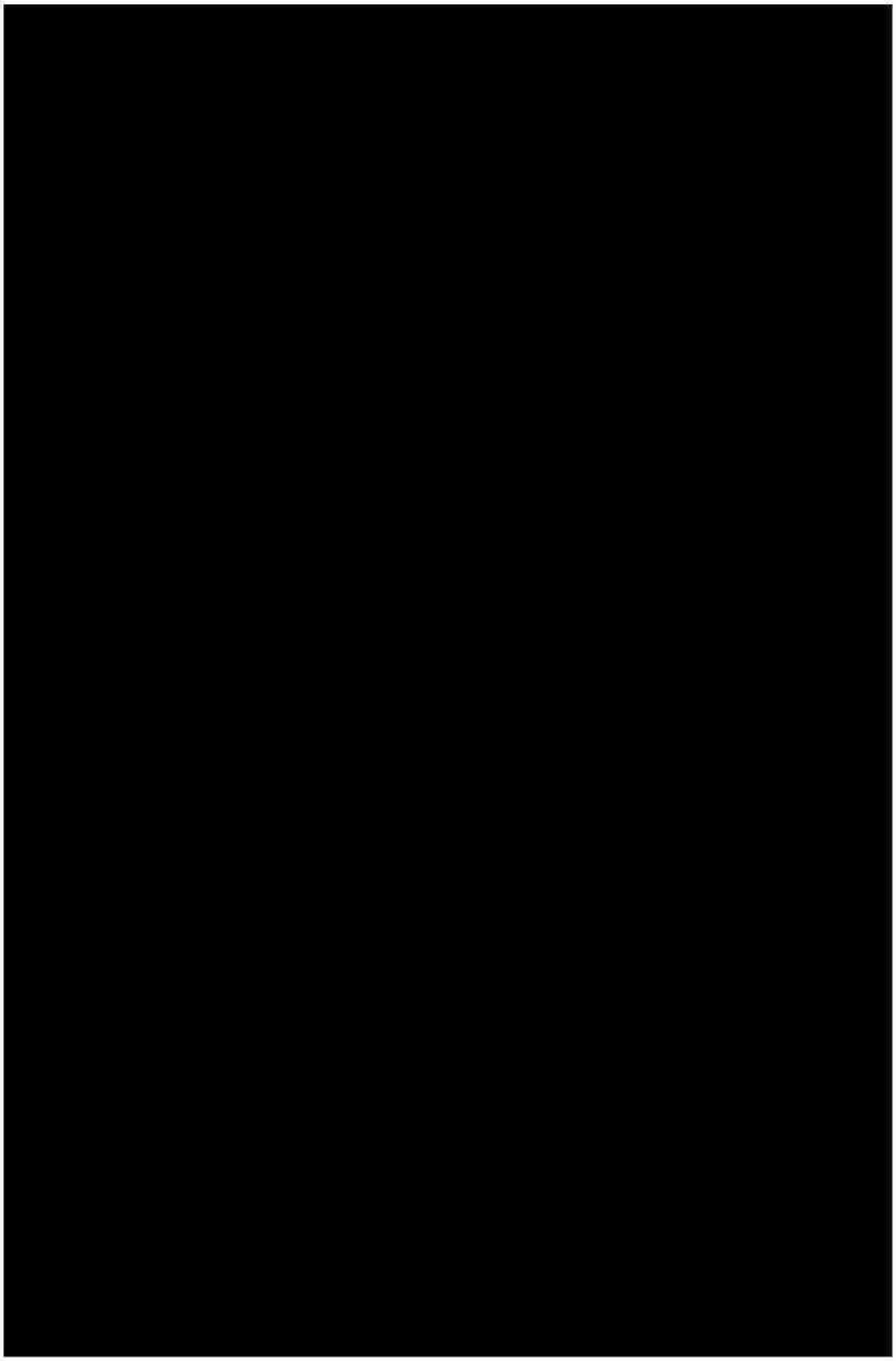
Signed [redacted]

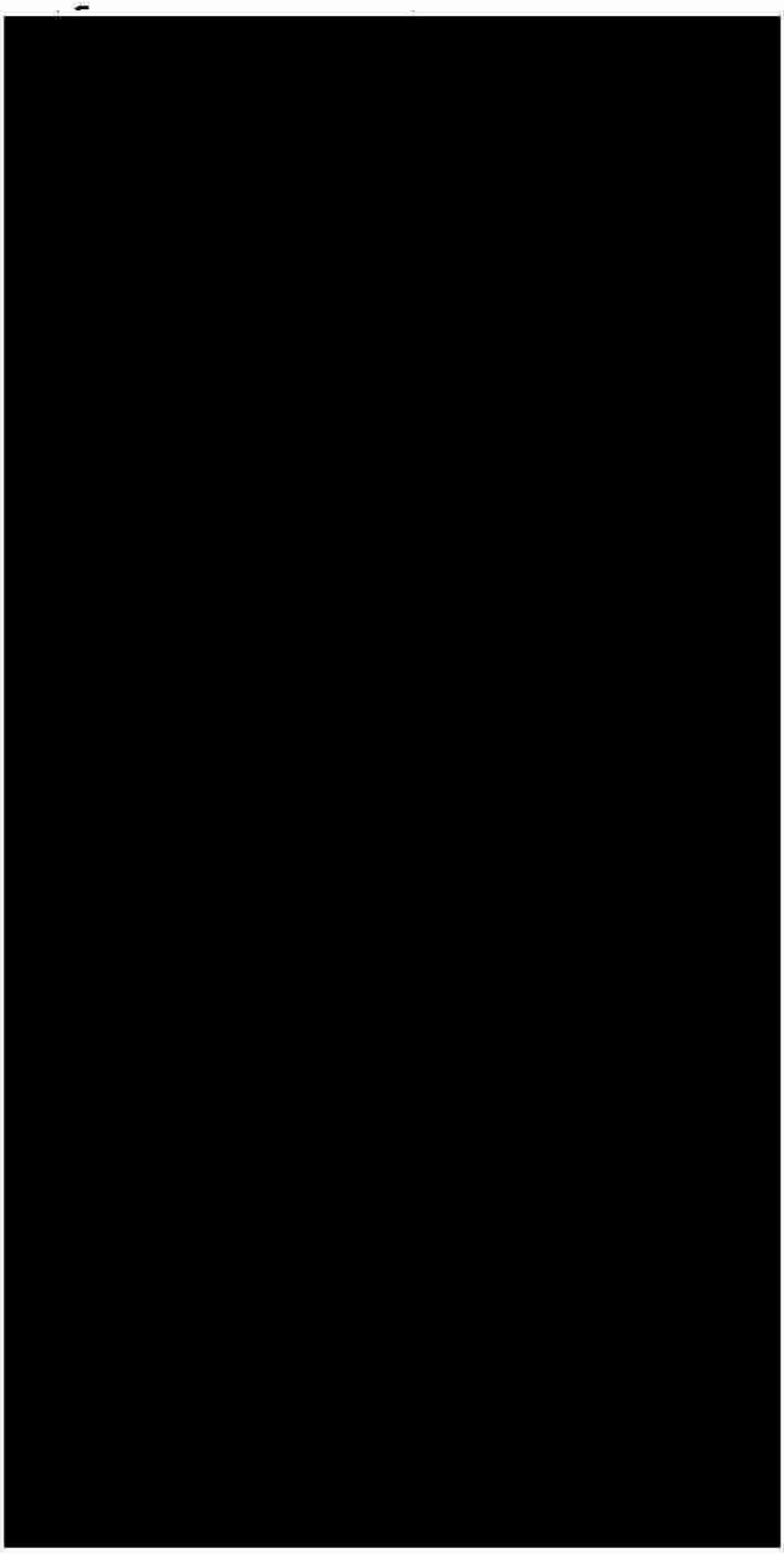
[redacted] Europe
Research & Development, Johnson & Johnson • MSD Europe
Date: 27 September 1999

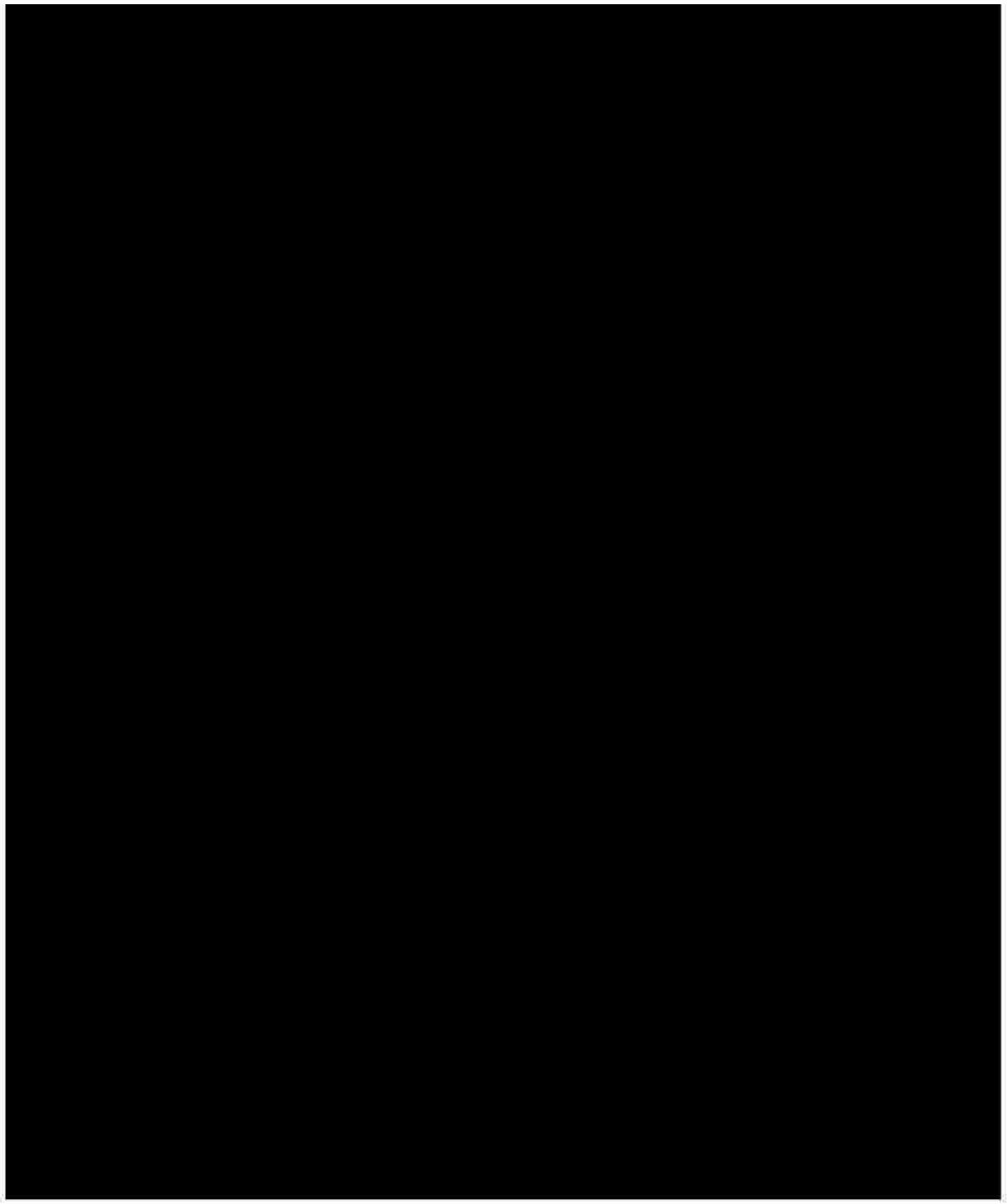
C:\WINDOWS\TEMP\Pep-addend-SGM.doc

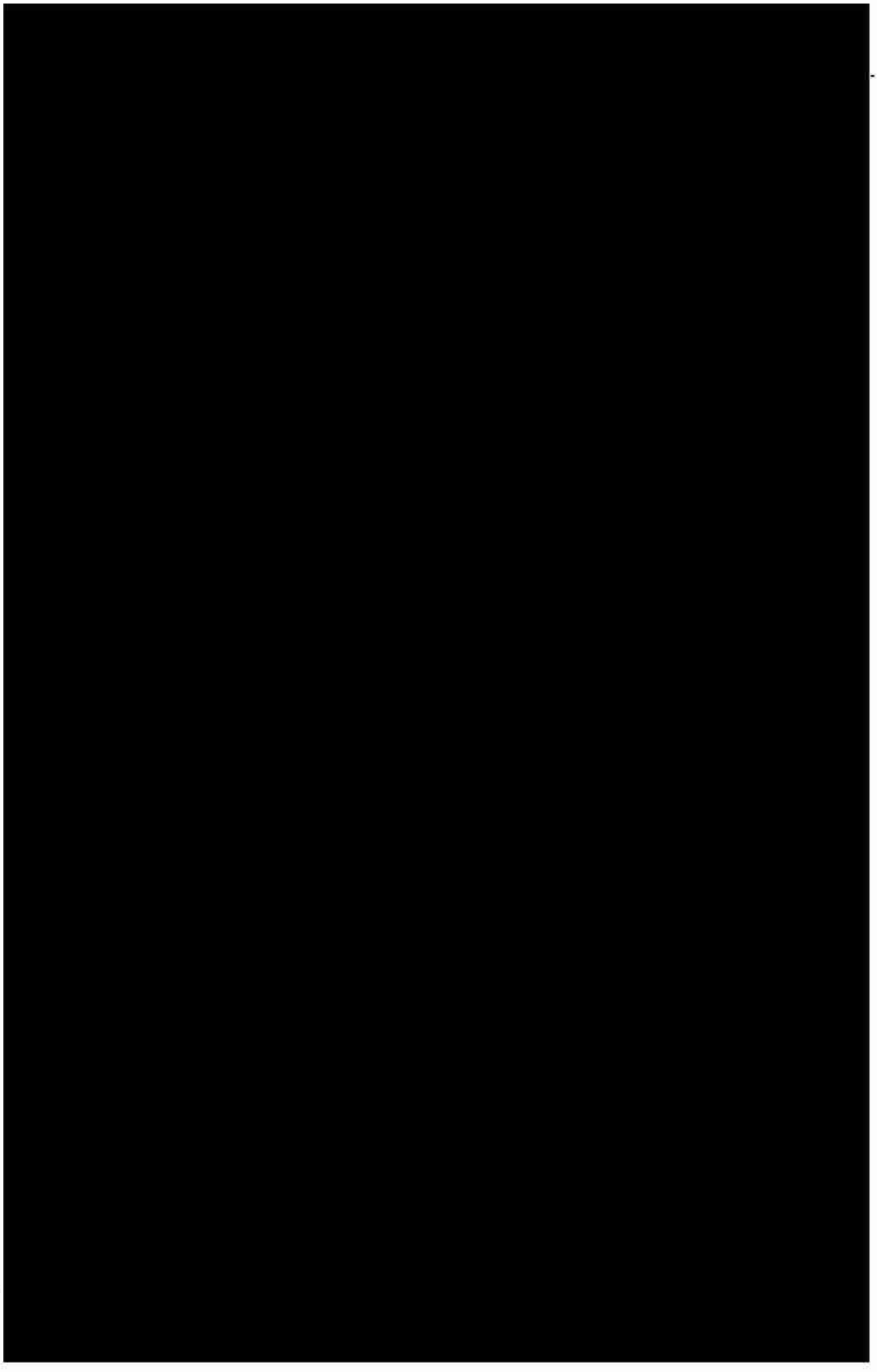
[redacted]

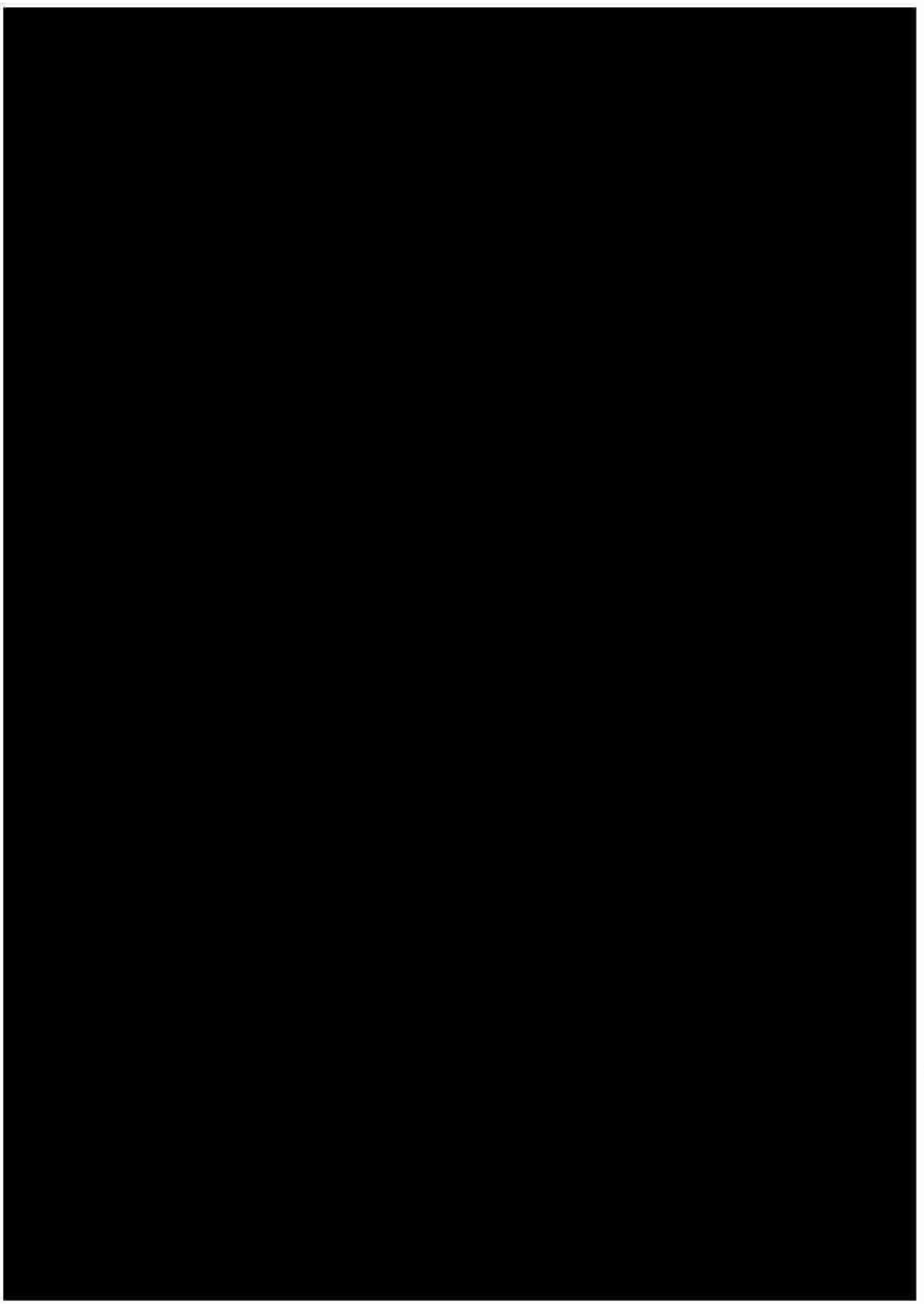


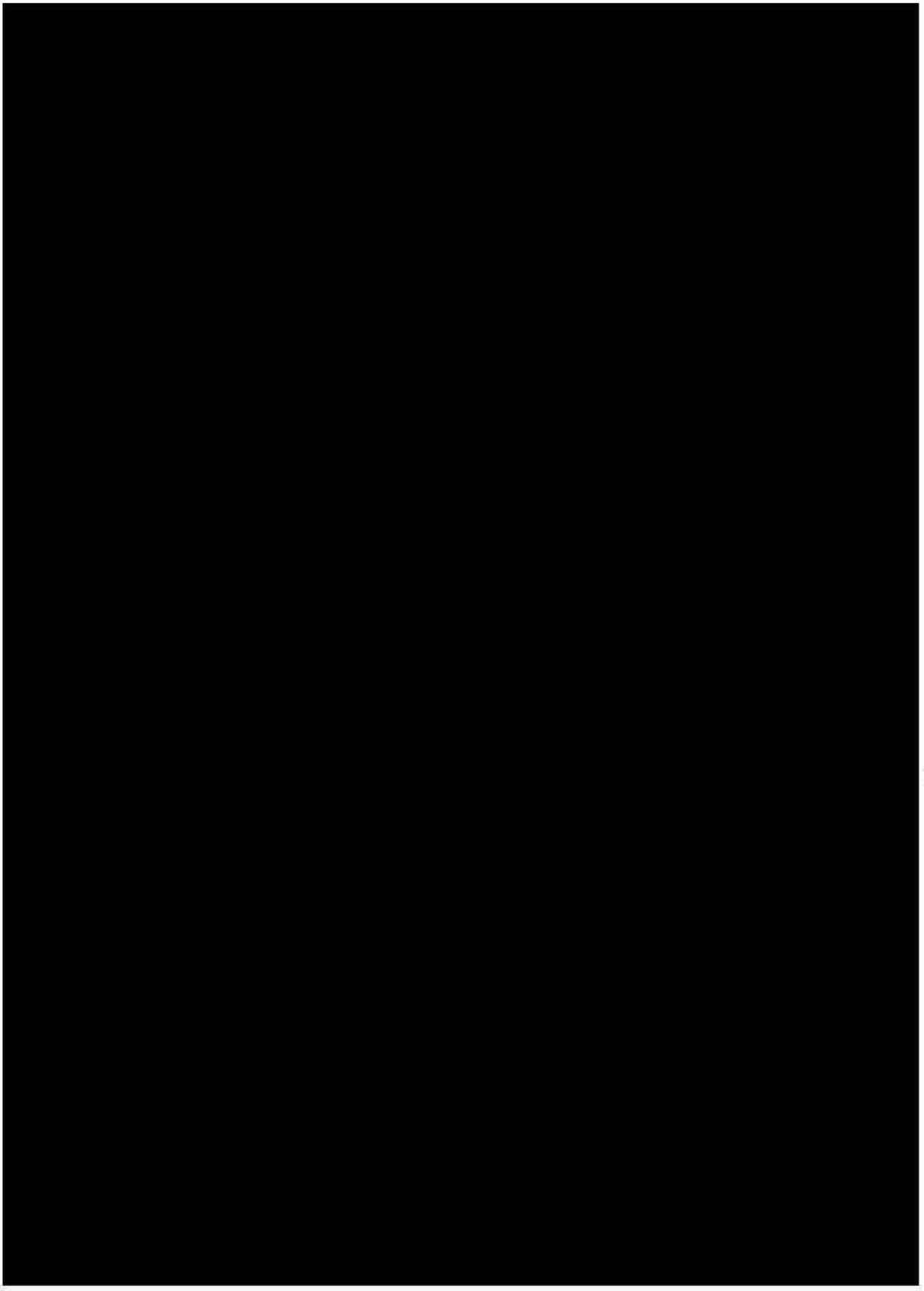












10 95

CONFIDENTIAL

PEPCID AC TABLETS AND CHEWABLE TABLETS

PL 0025/0312 AND 0025/0313

VARIATION APPLICATION TO CHANGE
THE LEGAL STATUS FROM
PHARMACY TO GENERAL SALES LIST
WITH REDUCED INDICATIONS

DATA TO SUPPORT THE APPLICATION

Johnson & Johnson • MSD Consumer Pharmaceuticals
Enterprise House
Station Road
Loudwater
High Wycombe
Bucks HP10 9UF

September 1999

PEPCID AC TABLETS AND CHEWABLE TABLETS
PL 0025/0312 AND 0025/0313
VARIATION APPLICATION TO CHANGE THE LEGAL STATUS FROM PHARMACY TO GENERAL SALES LIST WITH REDUCED INDICATIONS

DATA TO SUPPORT THE APPLICATION

CONTENTS

CONTENTS

1 INTRODUCTION

Famotidine is a potent histamine H_2 receptor antagonist. It selectively inhibits basal and stimulated gastric acid secretion and has no clinically significant activity at histamine H_2-receptors outside the gastrointestinal tract. The drug was first registered in the United Kingdom (UK) in 1987 for the treatment of gastric and duodenal ulcers and other acid related conditions with a normal maximum daily dose of 40 mg. At that time the formulations approved were Pepcid 20 mg and 40 mg tablets (PL 0025/0215 and 0025/0216, respectively).

Registrations of these formulations in a further 80 countries, including the major European markets, the USA and Canada, were achieved over the period 1984 to 1994, with similar indications.

Widespread use of the product over the years from the first launch in 1985 generated safety data which warranted a change in the legal status. To facilitate wider, less regulated use of famotidine, 10 mg film coated and chewable tablets were developed. The development programme included a full range of studies, including trials in 2000 patients with heartburn. The products, called Pepcid AC, were approved for supply through pharmacies in 1994 in the UK (PL 0025/0312 and 0025/0313, respectively).

The licensed indications for Pepcid AC are the short term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity, and prevention of these symptoms when associated with food and beverage, including nocturnal symptoms associated with the evening meal and expected to cause sleep disturbance. The maximum daily dose is 20 mg, and the maximum duration of treatment is 14 days.

The product has also been deregulated in at least 15 other countries from 1994 onwards, again including the major European markets, the USA and Canada.

Extensive use of Pepcid AC world-wide has underlined the product's safety and appropriateness for less supervised use. It is therefore now proposed, following MCA guidelines given in MAL 82, that the classification of famotidine be changed to General Sales List (GSL) for the treatment of heartburn, indigestion, acid indigestion and hyperacidity. It is not proposed that preventative use should be included. Dosages and the maximum duration of treatment are to be unchanged compared with the pharmacy (P) product.

It is also proposed to limit the maximum pack size for GSL use to 12 tablets, compared with 20 for the P product. This is the subject of a separate application.

2 PROPOSED REVISIONS IN DETAIL

The following changes are proposed to PL 0025/0312 and 0025/0313, held by Merck Sharp and Dohme Limited, and marketed as Pepcid AC by Johnson & Johnson • MSD Consumer Pharmaceuticals, and also as Boots Excess Acid Control by the Boots Company Ltd in the case of the standard tablets.

2.1 LEGAL CLASSIFICATION

Present P
Proposed GSL

2.2 THERAPEUTIC INDICATIONS

Present
The short-term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity.

Prevention of these symptoms when associated with food and beverage (drink) including nocturnal symptoms associated with the evening meal and expected to cause sleep disturbance.

Proposed (new wording is boxed)
P indications

The short-term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity.

Prevention of these symptoms when associated with food and beverage (drink) including nocturnal symptoms associated with the evening meal and expected to cause sleep disturbance.

GSL indications

The short-term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity.

2.3 POSOLOGY AND METHOD OF ADMINISTRATION

Note: the wording below refers to Pepcid AC film coated tablets. The wording for Pepcid AC chewable tablets is the same except for the instruction that the tablets are to be chewed.

Present
Adults and children 16 years of age or older:

Dosage: 10 mg

Dosage interval:
One tablet (10 mg) for symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity.

or

One tablet (10 mg) taken 15 minutes before consuming food and beverage (drink) known to be associated with or to provoke these symptoms. When these symptoms are expected to interfere with sleep, one tablet (10 mg) taken one hour before the evening meal.

Maximum intake in 24 hours: two tablets (20 mg)

Patients must seek medical advice if:
- symptoms fail to respond
- symptoms recur following self treatment with Pepcid AC
- if symptoms persist after two weeks treatment

The maximum treatment period is two weeks.

No dosage adjustment is necessary for the elderly.

Pepcid AC is not recommended for use in children less than 16 years of age.

Proposed (new wording is boxed)
Adults and children 16 years of age or older:

Dosage: 10 mg

Dosage interval:
One tablet (10 mg) for symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity.

In addition, for P use only:

One tablet (10 mg) taken 15 minutes before consuming food and beverage (drink) known to be associated with or to provoke these symptoms. When these symptoms are expected to interfere with sleep, one tablet (10 mg) taken one hour before the evening meal.

Maximum intake in 24 hours: two tablets (20 mg)

2.4 PROPOSED WORDING OF THE GSL ORDER

It is proposed that Table A of Schedule 1 of the principal order be amended to include:

Column 1	Column 2	Column 3	Column 4
Substance	Maximum strength	Use, pharmaceutical form or route of administration	Maximum dose and maximum daily dose
Famotidine	10 mg	Symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity	10 mg (MD) 20 mg (MDD)

2.5 SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The current SPCs for Pepcid AC film coated and chewable tablets are provided in Appendix 1.

The proposed SPCs for both formulations are provided in Appendix 2. These include the revised pack sizes which are the subject of a separate variation.

The proposal of 12 tablets for the largest GSL pack size fits well with the philosophy of GSL usage, as well as the 14 day maximum duration of treatment without referral to a doctor, specified in the SPC.

2.6 PATIENT INFORMATION LEAFLET (PIL)

The present PIL for Pepcid AC film coated tablets is provided in Appendix 3.

The proposed PILs for the Pepcid film coated and chewable tablet GSL packs are provided in Appendix 4.

The opportunity has been taken to rewrite the Pepcid PILs, taking into account the guideline on readability of the label and pack leaflet for medicinal products for human use.

2.7 LABELLING

The labelling text for Pepcid AC film coated tablets is provided in Appendix 5. The text for the chewable tablets is similar.

The proposed texts for the GSL packs for these products are provided in Appendix 6. Again, the opportunity has been taken to revise the label, taking into account the readability guidelines, as well as to modify strap lines. In addition, the statement "inactive ingredients include microcrystalline cellulose" has been deleted as this excipient is no longer required to be stated.

Pack mock-ups will be provided separately.

3 DATA TO SUPPORT THE PROPOSED CHANGES

3.1 ACID RELATED SYMPTOMS AND THEIR TREATMENT

The term "dyspepsia" encompasses a range of symptoms. Dyspepsia of all kinds is very common in the community with a prevalence of close to 40% over a six month period [1]. The great majority of these people will not have an identifiable cause for their symptoms and "non-ulcer" dyspepsia is about 10 times more common than peptic ulcer. The classification, by an international consensus group, of non ulcer dyspepsia into reflux-like, ulcer-like and dysmotility-like has been of great assistance in studying the response of particular symptom groups to treatment [2]. The management of acid related symptoms relies on either the inhibition or the neutralisation of gastric acid secretion by:

- proton pump inhibitors (PPIs): POM
- histamine H_2-receptor antagonists (H_2): P
- antacids (AAs): P and GSL
- alginates: P and GSL

3.1.1 H_2 Receptor Antagonists

H_2-antagonists were originally used exclusively on prescription as a treatment for peptic ulceration. However, patients with acid-related symptoms without damaged mucosa were increasingly prescribed ulcer-healing doses of the H_2-receptor antagonists to treat a range of dyspepsia symptoms. The hypothesis that such symptoms might respond to lower doses was proven through pharmacodynamic and efficacy studies. These were submitted in the POM to P applications for famotidine.

The doses which proved effective in the case of famotidine and ranitidine are:

Drug (mg/day)	Condition	
	Ulceration	Dyspepsia
Famotidine	20-40	10-20
Ranitidine	150-300	75-300

In the following summary, data on ranitidine, which has already been considered suitable for GSL use, is presented alongside information on famotidine.

3.2 CLINICAL PHARMACOLOGY

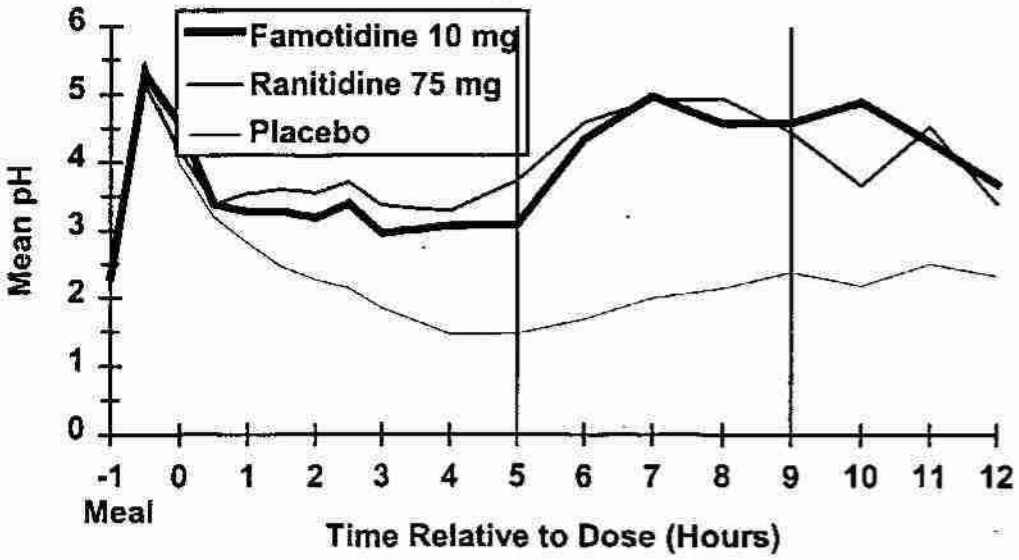
3.2.1 Pharmacodynamics

Previous dose ranging studies with famotidine [3] and ranitidine [4] demonstrated that both drugs could produce substantial inhibition of basal, pentagastrin-stimulated and meal-stimulated gastric acid secretion at approximately half the ulcer healing dose level.

A comparison of famotidine 10 mg and ranitidine 75 mg in normal volunteers [5] confirmed that both inhibited pentagastrin-stimulated gastric acid secretion profoundly in the early post dose period and that acid inhibition was still detectable up to nine hours after dosing.

The effect of these doses on gastric acidity after meals, during the peak time for occurrence of heartburn was also studied. When volunteers were given placebo, famotidine 10 mg or ranitidine 75 mg one hour after an evening meal, the profile of gastric pH for the two active drugs over the night-time period was strikingly similar [6]. Both produced significant effects on intragastric acidity for up to 12 hours in this model (Figure 1)

Figure 1



3.2.2 Pharmacokinetics

As a group, the H_2 receptor antagonists are rapidly absorbed after oral administration and peak plasma concentrations are reached within one or two hours. Oral bioavailability varies somewhat within the group with incomplete absorption reducing bioavailability to around 40% for famotidine and pre-systemic hepatic metabolism reducing ranitidine bioavailability to around 50%. Both famotidine and ranitidine are to a large degree excreted in urine unchanged. The elimination half-life for both is also similar at two to three hours, but may be prolonged for both in uraemic patients or elderly subjects with impaired renal function. Elimination may also be slower for ranitidine but not famotidine in patients with impaired hepatic function [7,8,9].

The target indications for these drugs are closely related to meals and therefore both have been studied to confirm that the co-administration of food does not interfere with their absorption and effect [7,8]. Pharmacokinetic and pharmacodynamic studies have also confirmed that antacids, which might be taken at the same time as the H_2 receptor antagonists by some consumers, do not have an appreciable effect on their absorption or activity [8,10].

3.3 EFFICACY IN THE TREATMENT OF ACID RELATED SYMPTOMS

Since ranitidine 75 mg and famotidine 10 mg are approximately equipotent in acid inhibition and produce their effects over a similar time course, comparable efficacy in reducing acid-related symptoms is to be expected. Both manufacturers have conducted extensive clinical programs concentrating on the symptoms of heartburn and acid reflux. The reasons for this are:

- these are the most clearly acid-related symptoms
- they are present in a high proportion of patients with dyspepsia
- they are the most easily described and recognised symptoms for patients

However, studies in heartburn are difficult because most episodes are self-limiting and because temporary clearance of acid from the oesophagus (eg by swallowing water) will produce a temporary reduction in symptoms. Taken together, these factors explain the very high placebo responses (typically 60%) in studies of this symptom complex. This also explains why there was an almost complete lack of data regarding the efficacy of antacids in this condition until the H_2 receptor antagonist clinical programs included antacids as active comparators to validate the models used [11].

Although carefully conducted clinical studies were necessary to establish efficacy for the H_2 receptor antagonists in treating individual episodes of heartburn, these studies do not fully illustrate the particular benefits of this class of agents in this condition. The long duration of antisecretory activity available with low dose H_2 receptor antagonists offers the prospect that a single dose will prevent the return of heartburn, which is typically episodic but relapsing in nature.

Two more recently published studies with low dose famotidine illustrate that a single evening dose can provide significant reduction in heartburn suffering during an overnight period [12] and that when a heartburn episode is treated during the day, sufferers are protected from a return of their symptoms following their next meal [13]. Thus the prolonged effect of famotidine on intragastric acidity can translate into a meaningful benefit for heartburn sufferers.

3.4 RECOGNITION OF SYMPTOMS

Low doses of the H_2 receptor antagonists have been shown to be effective in the treatment of heartburn and reflux-like symptoms and it is this group of symptoms which are proposed as the indications for self-medication with famotidine.

Approximately one in three apparently healthy people report heartburn but only one in 10 suffer more than once a week. Typically heartburn is intermittent with a high proportion of episodes (74%) occurring in relationship to a recent meal [14]. Sufferers can often identify particular foods and drinks which tend to trigger their symptoms but they will not always suffer when they consume them [15].

Reflux symptoms can be reproduced by instilling acid into the lower oesophagus (the Bernstein test) and symptoms disappear when this acid is cleared from the oesophagus by swallowing water. This sensitivity of the lower oesophageal mucosa to acid is the underlying mechanism for heartburn caused when acid gastric contents reflux into the oesophagus, typically after meals [16].

Heartburn and acid reflux are the most clearly acid-related of all dyspepsia symptoms and responses to treatments which reduce intraluminal acid are reliable. The close relationship of these symptoms to meals provides an additional aid to recognition. Self-medication with antacids for these symptoms is common and it is therefore established that they may be readily recognised by consumers.

Although other conditions may present with acid-related symptoms, the pattern of presentation and in particular the duration of symptoms and response to treatment allows differentiation from simple heartburn (see Section 3.6).

3.5 DURATION OF SELF-MEDICATION

3.5.1 Typical Pattern and Frequency of Symptoms

Medicines available for self medication are often subject to warnings regarding the maximum desirable period of self-medication without medical supervision. These warnings reflect the normal self-limiting nature of the symptom under consideration. For example most treatments for headache advise the sufferer to consult a doctor if symptoms persist and require treatment for more than a few days. It is important to consider the normal pattern of symptoms for simple acid-related symptoms in order to recommend suitable guidelines for treatment duration.

Simple heartburn and acid reflux is typically episodic, with episodes separated by several days or weeks in the majority of cases [14]. Each individual attack may consist of several periods of suffering, typically after meals and on retiring to bed. The underlying mechanism for this pattern is likely to be:

- the lower part of the oesophagus becomes irritated when is exposed to refluxed acid which is not cleared [16]

- subsequent acid exposure produces symptoms (this usually occurs after meals when the stomach is stimulated to produce acid and stretching of the stomach makes reflux more likely, certain foods and drinks will also relax the lower oesophageal sphincter [17])

- reduced acid exposure through dietary adjustment, attention to posture and treatment of symptoms reduces oesophageal irritation and symptoms subside [18]

In these circumstances, treatment is used to help break the cycle of acid exposure and symptom generation. Usage studies performed in the US before launch [19] and market research in Sweden in patients self-medicating with famotidine 10 mg [20] have confirmed that most patients take single doses of H_2 receptor antagonists on a day when they suffer [19] and that these doses are separated by a median of eight days [20].

3.5.2 Upper Limit for Self-Medication

If patients suffer frequently and require repeated dosing for long periods, then it is likely that they have a condition other than simple heartburn. For this reason an upper limit of two weeks continuous dosing is reasonable. This recommendation is intended to improve the likelihood of patients with more serious underlying conditions seeking medical advice.

Famotidine for GSL usage will be supplied in a maximum pack size of 12 tablets which would provide only six days' continuous treatment at the maximum daily dose. This reflects the expected intermittent pattern of use and provides an additional incentive for sufferers not to treat for extended periods

3.6 MASKING OF MORE SERIOUS DISEASE

The concern that the availability of the H_2 receptor antagonists for self-medication may mask the presence of more serious disease in some patients has been examined by Holt in a review paper [21] and the major considerations are addressed below.

The other, more serious conditions, which might present with heartburn and acid reflux are: ulceration of the oesophagus, stomach or duodenum and malignant tumours of the oesophagus or stomach. The risks associated with a delay in the diagnosis for each of these conditions are reviewed in turn.

3.6.1 Peptic Ulceration

3.6.1.1 General

Some patients with heartburn and acid reflux will have mucosal damage amounting to ulceration. If these patients choose to self-medicate there are two general safety questions:

- Will they have adequate control of symptoms while the lesion progresses and worsens?
- If the ulcer persists will they be at increased risk of ulcer complications such as bleeding or perforation?

In one published study [11], patients with heartburn three times a week were endoscoped before and after a four week period of double-blind medication with famotidine 5, 10 or 20 mg, antacid 11 meq, or placebo taken as needed. Of the patients with lesions in the duodenum, stomach or oesophagus the majority in all patient groups either remained unchanged or healed; and almost none showed worsening. These data are very reassuring that even frequent sufferers with underlying mucosal disease do not show adverse changes in endoscopic appearance over a four week period of self medication.

Complication rates during short term treatment of known ulcers are very low. In the numerous clinical studies where patients with ulcers were randomly assigned to placebo no complications were observed [22]. The risks of ulcer complications occurring during inadvertant short term treatment with intermittent H_2 receptor antagonists are thus extremely small.

3.6.1.2 Erosive Oesophagitis

Although symptoms do not always correlate well with severity of oesophagitis, patients with severe erosive disease on endoscopy usually have a long history of symptoms . These patients are at risk of developing strictures or the pre-malignant Barrett's oesophagus although even severe oesophagitis has very little effect on life-expectancy [23]. Treatment is aimed at reducing acid reflux to low levels with high doses of potent antisecretory drugs.

Low doses of the H_2 receptor antagonists would at best provide partial and short-term relief to patients with severe erosive disease. Since the propensity to reflux would remain, symptoms would return promptly when the H_2 receptor antagonist was stopped. Even if the patient with erosive disease achieved some healing with self selected famotidine, the return of symptoms should signal to the patient that a medical consultation is needed. The possibility that patients will ignore this advice and continue to self medicate for long periods is no greater than with the existing cheaper antacids which are currently available.

3.6.1.3 Gastric and Duodenal Ulcer

Heartburn and acid reflux are recognised but relatively uncommon symptoms of ulceration below the oesophagus. Ulcers of the duodenal and gastric mucosa require four to eight weeks of full dose H_2 receptor antagonists to produce healing and therefore it is extremely unlikely that short term intermittent doses of the same agents would produce complete healing. It follows that the ulceration would continue to produce symptoms when treatment was interrupted.

The warnings on the proposed labels indicate that persistence of symptoms should alert the patient to the need for a medical opinion. Since similar short-term relief of symptoms might be expected with existing antacids, the possibility of delayed diagnosis will be no greater than at present.

3.6.2 Malignancy

Malignancy of the upper gastrointestinal tract is much less common than ulceration which is in turn considerably less common than symptoms without ulcers [24]. The commonest malignancy, gastric cancer, is extremely unusual below the age of 45 but the incidence rises in the sixth and subsequent decades of life [25]. Presenting symptoms vary but heartburn alone is a relatively uncommon presentation (4% in a recent series) and warning symptoms such as weight loss (12%), dysphagia (24%) and anaemia (17%) may be present [26].

Long-term studies have established that H_2 receptor antagonists do not induce or encourage the development of gastric malignancy [27]. If a tumour is already present, particularly a malignant ulcer, the associated symptoms might respond to medicines which reduce gastric acidity. Concern has been expressed that this might delay the diagnosis and adversely affect the outcome.

Gastric cancer develops over a long period of time: an 'early'(ie mucosal or submucosal) tumour doubles in size over one-and-a-half to 10 years. More advanced tumours may double in size in two months to one year [26]. Paradoxically, this leads to the observation in several series that the earliest and most treatable tumours tend to present with longer symptomatic histories [26, 28]. However, most tumours are advanced when they present [29] and the aim is to reduce the time to definitive diagnosis and surgical treatment in the hope that this will influence outcome.

In several series from the UK [26] and Germany [30], there appears to be no correlation between the delay in diagnosis (measured from first symptoms) and the stage of disease (which is the best predictor of outcome). There is therefore no evidence that even long delays are likely to influence the course of gastric cancer significantly [28]. Nonetheless, early self-referral should be the aim and the portion of delay attributable to the patient (which varies from two weeks in the Leeds series to 12 weeks in the Munich series) may be amenable to patient education.

The proposed leaflet highlights the warning features which might identify those patients requiring investigation. These include: new or recently changed symptoms in patients aged 45 years or older, unintended weight loss, and difficulty swallowing. Symptoms in malignancy, once present, tend to continue and thus persistence of symptoms alerts the patient to consult.

A recent survey[31] of all gastric cancer cases in a region of the UK over a seven year period showed that only a small proportion (7.8%) presented in patients younger than 55 years. All but one of these had warning signs or symptoms and the proposed leaflet for famotidine would have helped identify these in the majority of cases. These data show that the leaflet warnings proposed are important health messages, but they also provide reassurance that uncomplicated dyspepsia (ie without warning signs) in the under 55 year age group is almost invariably due to non-malignant causes.

In Denmark the H_2 receptor antagonists were transferred to non-prescription status six years ago, in full prescription strength and with a maximum duration of use of four weeks [32]. Careful monitoring since this change has not indicated a change in the pattern of referrals for endoscopy [33]. However, the percentage of patients truly taking the H_2 receptor antagonists without supervision is small (estimated at 10%) so the power of these studies to detect changes is limited.

The incidence of gastric cancer is so low in Western countries that it is difficult to measure changes in incidence and the influence of treatment changes would be difficult to detect. However, a decision analysis model has been developed to examine the impact of non-prescription H_2 receptor antagonists on risk and benefit to dyspepsia sufferers in the US [34]. In this model, of the 5.7 million patients per three months suffering dyspepsia, 5116 or 0.1% would have gastric cancer. The authors calculated that 300 more of these would self-medicate as a result of the availability of the H_2 receptor antagonists, but that this would not change the median time between symptom onset and physician consultation.

In summary, gastric cancer progresses slowly over many years and most often causes symptoms when it is already advanced. Consequently, even many weeks delay in diagnosis are extremely unlikely to influence overall outcome. Short term treatment with low dose H_2 receptor antagonists or antacids may give some temporary relief from symptoms, but symptoms will return and persist. The proposed leaflet for famotidine contains specific advice about treatment duration and warnings on the particular symptoms which warrant early investigation to exclude cancer.

3.7 IMPACT OF H_2 RECEPTOR ANTAGONISTS SWITCHING ON PRESCRIPTION RATES

3.7.1 UK

Prescription rates are a good surrogate marker for the number of consultations for particular conditions. Data are available from commercial databases which track market shares (data presented below are all IMS sourced). However, a recent paper [35] from the UK looked at the reasons for prescriptions as well as the changes in proportions for types of medication. Over the years 1991 to 1996 they documented a marked rise in scripts for the proton pump inhibitors with a large proportion being written for reflux symptoms. In contrast numbers of scripts for the H_2 receptor antagonists declined (by 12.5%) with non-specific dyspepsia accounting for 43.6% of these.

These trends were unaffected by the switch of the low-dose H_2 receptor antagonists which happened in 1994 (for cimetidine and famotidine and one year later for ranitidine). However, the H_2 receptor antagonists captured only a small percentage only of the self-medication UK market.

3.7.2 Sweden

A post-marketing study was conducted by Pharmacia and Upjohn (the licence holders) after famotidine 10 mg became available for self medication of heartburn and acid reflux in Sweden. As well as examining the impact of this switch on consultations for upper gastro-intestinal complaints, the study followed a cohort of 329 self-medicating heartburn sufferers for one year after a consultation in pharmacy.

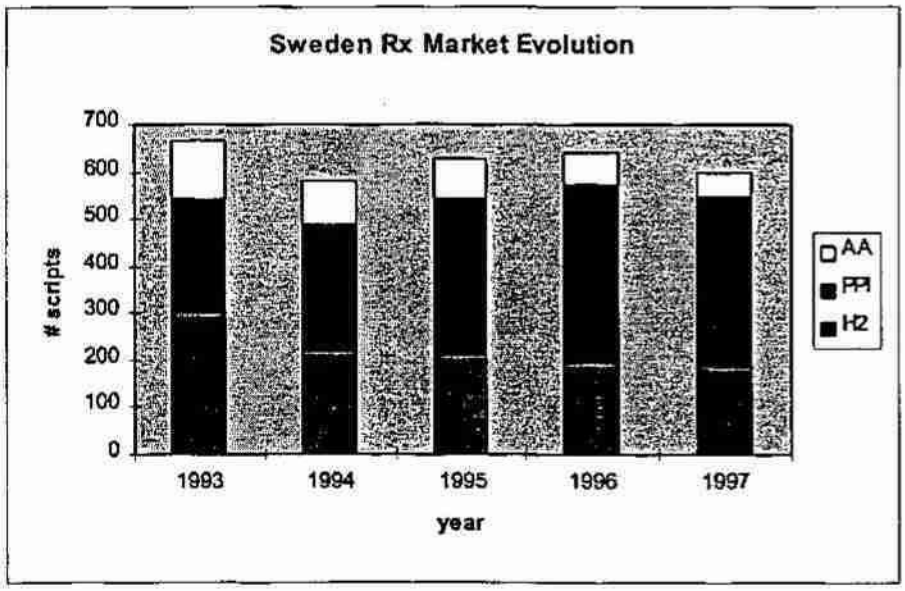
Total prescriptions for H_2 receptor antagonists showed no marked change in the years following the switch of famotidine and ranitidine (which occurred one year later). Although there was a small reduction in prescriptions for antacids, this trend was apparent before the switch. Over the same time interval the overall prescriptions for upper GI complaints grew with proton pump inhibitors responsible for much of the volume. The authors conclude that the switch of the H_2 receptor antagonists has not adversely affected consultation behaviour as determined by prescriptions written.

The cohort study showed that the great majority (95%) of sufferers presenting to pharmacies with heartburn were not new sufferers and many had self-medicated before (66%) or had had a prescription for similar symptoms(29%). Pharmacy advice seemed to be well accepted with over half of the cohort claiming to have modified their lifestyle at one month follow-up.

At long-term follow up (one year) a high proportion of the population (87%) were still suffering their symptoms. The tendency of patients to consult their physician was not affected by choice of self-medication with 23% of famotidine treated patients and 27% of those receiving other self-medications. There was no apparent delay of diagnosis in this study and no malignancies occurred.

Importantly, this study, although small, showed that the choice of an H_2 receptor antagonist had no apparent influence on the tendency to consult (Figure 2).

FIGURE 2



3.8 EXPERIENCE IN THE USA

The most relevant experience with respect to the proposed P to GSL switch in the UK is the US where famotidine can be self-selected in the same way as is now proposed should be the case here.

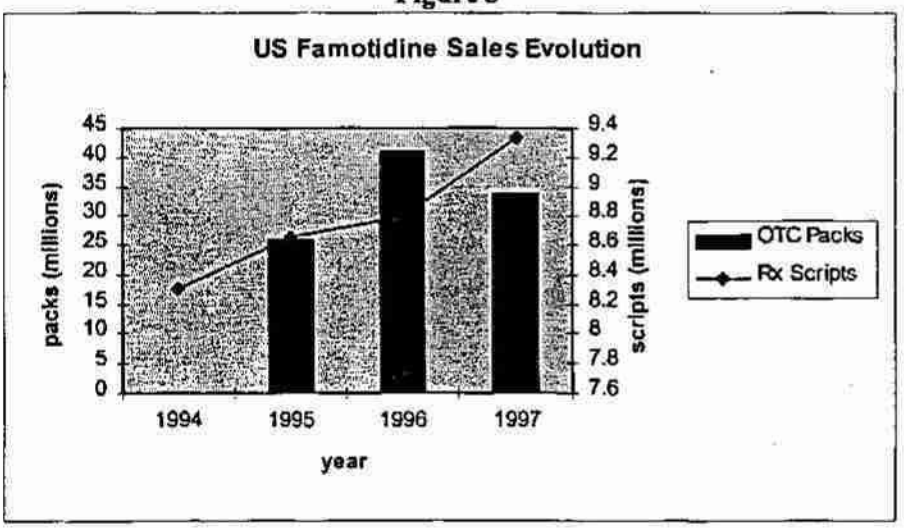
The switch of the H_2 receptor antagonists expanded the self-medication sector substantially.

They now have over 30% of the whole upper gastrointestinal self-medication category (34 million packs were sold in 1997). Patients can purchase large pack sizes (up to 80 tablets) without the intervention of the pharmacist. This market therefore represents an environment in which these factors - together with the cost of physician consultation - might be expected to result in a greater tendency to self medicate rather than consult.

It would be of concern if patients were to alter their behaviour in favour of non-consultation. If this were to happen to any substantial degree it would be apparent in changes in the scale of prescriptions for upper gastrointestinal conditions.

This expectation is not borne out by experience in the years since the switch. This is perhaps best illustrated by the growth in prescriptions for famotidine which occurred at the same time as the very rapid expansion of the self-selection market occasioned by its switch in June 1995. Famotidine remained on patent during the period so these data are not confounded by patent status changes which affect the interpretation of data on cimetidine over the same period. (Figure 3).

Figure 3



Prescription data from markets where the H_2 receptor antagonists have been successful, including the USA where self selection is the norm, do not show any impact of the switch on patients' tendency to consult their physician. This suggests that the H_2 receptor antagonists take market share from existing non-prescription remedies without influencing consulting behaviour which is governed by other factors.

3.9 EXPOSURE TO FAMOTIDINE

The following figures are total as famotidine is only available from a single company.

3.9.1 20 mg and 40 mg Tablets

These tablets, for prescription only use, have been registered in 81 countries, as follows:

Famotidine Tablets (20 and 40 mg) Licensed Status

Country	Approval Date	Country	Approval Date
Italy	21 Sep 84	Belgium	2 Mar 88
Japan	31 Jan 85	Togo	10 Mar 88
Switzerland	14 Jun 85	Pakistan	21 Apr 88
Germany	5 Aug 85	Oman	1 Jun 88
Colombia	29 Nov 85	Australia	1 Jul 88
Portugal	4 Dec 85	Luxembourg	14 Jul 88
Greece	29 Apr 86	Kuwait	1 Aug 88
New Zealand	25 Aug 86	Cameroon	26 Oct 88
Mexico	26 Aug 86	Bahrain	27 Oct 88
Canada	9 Oct 86	Gabon	11 Nov 88
USA	15 Oct 86	Yemen	1 Dec 88
Denmark	27 Nov 86	Sri Lanka	13 Dec 88
Holland	2 Feb 87	Zaire	29 Dec 88
Spain	5 Feb 87	South Africa	11 Jan 89
Costa Rica	12 Feb 87	Mauritania	20 Feb 89
France	3 Mar 87	Tunisia	28 Feb 89
Mayotte	3 Mar 87	China	7 Mar 89
Reunion	3 Mar 87	Mauritius	8 May 89
Ivory Coast	11 Mar 87	Singapore	1 July 89
Cyprus	13 Mar 87	Austria	19 Sep 89
Benin	14 Mar 87	Norway	28 Sep 89
Argentina	20 Mar 87	Aruba	2 Oct 89
Sweden	27 Mar 87	Kenya	26 Nov 89
Ecuador	20 Apr 87	Zimbabwe	29 Dec 89
El Salvador	20 May 87	Morocco	9 Jan 90
Guatemala	20 May 87	Saudi Arabia	24 Jan 90
Honduras	20 May 87	Turkey	7 Mar 90
Panama	20 May 87	Malaysia	19 Mar 90
Iceland	15 Jun 87	Senegal	28 May 90
Finland	8 Jul 87	Thailand	28 May 90
Venezuela	5 Aug 87	Nicaragua	1 Jul 90
Brazil	24 Aug 87	UAE	5 Oct 90
Peru	7 Sep 87	Burkina Faso	6 Nov 90
UK	9 Sep 87	Bolivia	11 Jun 91
Ireland	12 Oct 87	Ghana	29 May 92
Qatar	1 Nov 87	Mali	6 Jun 92
Aruba	2 Dec 87	Philippines	31 Jul 92
Curacao	2 Dec 87	Guinea	3 Nov 92
Jordan	1 Jan 88	Niger	21 Jan 93
Hong Kong	13 Jan 88	Indonesia	7 Feb 94
Congo	12 Feb 88	Armenia	11 Nov 94

This list is not necessarily exhaustive

The number of famotidine tablets prescribed between January 1995 and July 1999 was approximately 3567 million. Due to varying dosages and durations of therapy, it is difficult to estimate the number of patients exposed. However, it must be in excess of 30 million.

3.9.2 10 mg Tablets

These tablets, for non-prescription use, have been registered in over 15 countries since 1994 as follows:

Country	Approved Date
UK	04 Feb 94
Sweden	09 Mar 95
USA	28 Apr 95
Holland	19 May 95
Australia (20 mg)	31 May 95
Hong Kong	18 Jul 95
Mexico	23 Oct 95
Canada	14 Feb 96
France	21 Mar 96
Belgium	20 Oct 98
Finland	13 May 96
Norway	14 Jan 97
Argentina	23 May 97
Spain	14 May 98
Germany	10 Jun 99

This list is not necessarily exhaustive

In the USA only, famotidine is available on a basis equivalent to GSL in the UK.

The number of packs of non prescription famotidine tablets between 1994 and 1997 was approximately 115 million. Again, due to varying dosages and durations of therapy, it is difficult to estimate the number of patients exposed. However, if each patient purchased two packs, this would equate to around 50 million people. This is probably an underestimate.

3.10 SAFETY

3.10.1 Adverse Event Profile

A periodic safety update report (PSUR) on the 20 mg and 40 mg strengths covering the period April 1989 to December 1994 was submitted to the MCA with the PL renewal applications for Pepcid AC 10 mg film coated and chewable tablets on November 3 1998.

A supplement covering the period January 1995 to August 1999 is now available and is provided in Appendix 7.

Most of the reactions reported during the period of this safety supplement are either already listed or represent situations for which conclusions cannot be drawn. The supplement provides reassurance that Pepcid 20 and 40 mg remain generally well tolerated. Analysis of the data supports the adequacy of the SPC in terms of clinical data, prescribing information, and product safety.

More pertinent, a safety supplement covering non prescription use for the period January 1995 to August 1998 was also submitted at the time of the renewal.

A supplement covering the period September 1998 to August 1999 has now been generated to support this variation application, and is provided in Appendix 8. A summary table of events for the period January 1995 to August 1999 has been generated from these sets of data and is provided in Appendix 9.

The following table further summarises the events for the whole period.

Body System	Number of Episodes*	Number of Events
Body as a whole/site unspecified	2981	3152
Cardiovascular	304	321
Digestive	3072	3497
Endocrine	5	5
Eyes, ears, nose and throat	293	303
Haemic and lymphatic	23	24
Hepatobiliary	17	23
Immune	22	23
Metabolism and nutrition	153	162
Musculoskeletal	215	233
Nervous	960	1015
Psychiatric	248	289
Respiratory	149	157
Skin and appendages	846	1052
Urogenital	296	323
Total	9584	10579

* An episode may include one or more events

This section reviews the overall profile of the H_2 receptor antagonists, and famotidine and ranitidine in particular, in relation to categories of adverse events, potential for interactions and safety in special patient groups.

Inevitably, this knowledge derives mainly from reports relating to prescription doses and usage. The truth of the prediction that the adverse event profile for famotidine was suitable to allow non-prescription use is also explored.

3.10.1.1 General

The H_2 receptor antagonists are very well tolerated drugs and famotidine and ranitidine appear to be rather better tolerated than cimetidine. In clinical studies the overall incidence of adverse events for both drugs is around 5%, which is similar to that in placebo control groups. As well as very large databases from clinical studies and post marketing surveillance, world-wide usage of both drugs extends to many tens of millions of patients treated. Thus, the H_2 receptor antagonists have extremely well characterised adverse event profiles.

The low incidence of adverse events with this class reflects the limited function of H_2 receptors in organs other than the stomach. Adverse effects which are not mediated through blockade of these receptors are specific to each compound. Thus famotidine and ranitidine do not share some of the well known adverse effects of cimetidine.

Serious adverse events with the H_2 receptor antagonists are very rare and often the drug relationship is difficult to ascertain. The most important categories of event are considered below.

3.10.1.2 Haematology

Isolated cases of thrombocytopaenia, leukopaenia and pancytopaenia (all usually reversible) have been recorded as adverse effects with famotidine or ranitidine. Often patients had coexisting illnesses or concomitant medication which might have been responsible for the effect. The risk of these events in prescription usage is very small and has been further reduced in the circumstances of intermittent self-medication with low doses of these drugs. Of the over 10,000 adverse events recorded for non-prescription use, there are only four cases of leucopaenia (listed as leucopaenia:2, or leucocytes decreased:2) and one of thrombo-cytopaenia.

3.10.1.3 Liver Dysfunction

Rare cases of transiently raised liver enzymes, hepatitis and jaundice have been associated with all of the H_2 receptor antagonists. Again, drug causality is difficult to assess and concurrent alcohol consumption, infectious hepatitis and other diseases are likely to have been the cause in some of the reported cases. In almost all cases the changes were reversible.

In non-prescription usage, hepatobiliary problems have accounted for only 0.2% of adverse events reported (17 events).

3.10.1.4 Neuropsychiatric Reactions

Headache seems to occur occasionally with all the H_2 receptor antagonists and in clinical trials was the commonest adverse event with low dose famotidine (4.1%), followed by dizziness (1.3%). In non-prescription usage, headache and migraine account for 3.9% (416 events) and 3.5% (375 events) of all reported events, respectively

Confusional states and other acute psychiatric effects, particularly in elderly or very sick patients (eg in renal failure) have been reported rarely with cimetidine but seem to be much less common with famotidine and ranitidine. In non-prescription usage with famotidine, confusion *per se* has accounted for 0.2% (21 events) of the adverse events reported.

3.10.1.5 Hypersensitivity Reactions

All of the H_2 receptor antagonists have rarely caused hypersensitivity reactions such as urticaria, angioedema, bronchospasm and arthralgia. For famotidine, non-prescription usage has resulted in 0.2% of all events reported being for the immune system (23 events).

3.10.1.6 Hormonal Effects

Cimetidine has several properties which affect hormonal functions and can result in adverse effects: the drug enhances the secretion of prolactin, binds to androgen receptors, and increases the circulating levels of oestradiol in men through inhibition of its liver metabolism. Loss of libido, impotence and gynaecomastia are sometimes seen in patients receiving long-term and high-dose treatment.

In contrast both famotidine and ranitidine do not alter plasma hormone levels and do not bind to androgen receptors. Effects on sexual function are correspondingly very rare with these drugs.

In non-prescription usage, amongst all adverse events, reporting rates have been loss of libido: 0.1% (12 events), impotence: 0.3% (29 events), gynaecomastia: 0.1% (listed as this, or as breast enlargement: 9 events), and sexual dysfunction: 0.1% (5 events).

3.10.1.7 Cardiovascular Effects

Since cardiovascular disease is highly prevalent in middle aged Western populations, it is not surprising that serious adverse events such as myocardial infarction appear in the databases for all the H_2 receptor antagonists. However H_2 receptors are present in the heart and are inotropic. Rare reports of heart failure arrhythmias and hypotension have been reported with all the H_2 receptor antagonists and almost all of these have occurred with intravenous use in seriously ill patients. Coexisting cardiac disease or other disease was evident in many of these cases.

The risk of cardiac adverse events appears to be extremely small even with intravenous use, and with lower doses taken orally, any risk is remote.

In non-prescription usage, the most common cardiovascular system events have been hypertension (listed as this, or as increased blood pressure: 1.1%, 121 events) and palpitation (0.5%, 52 events) and tachycardia (0.6%, 61 events).

3.10.2 Drug Interactions

Cimetidine inhibits the activity of Cytochrome P450 and so slows the metabolism of the many drugs that are handled by the hepatic mixed-function oxidase system. In contrast neither famotidine or ranitidine inhibit the mixed function oxidases and therefore do not share the potential to interact with drugs by this mechanism. Studies with both drugs have confirmed that they do not interfere with the metabolism of drugs which have been shown to interact with cimetidine.

Some studies have claimed to show that some H_2 receptor antagonists at prescription strength (cimetidine and ranitidine but not famotidine) can increase blood alcohol levels by interfering with gastric alcohol dehydrogenase, but these data are contradicted by a large body of studies showing no effect. A review of all the data in 1993 concluded that very little, if any, metabolism of ethanol occurs in the gastric mucosa and that there was no clinically significant interaction with any of the drugs [36].

3.10.3 Effects in Overdose

Both ranitidine and famotidine have a very large margin of safety in overdose, and no serious effects directly attributable to the drugs have been recorded when overdose has occurred.

Over 800 mg/day of famotidine (20 times the normal maximum daily prescription dose) has been administered for many months in patients with Zollinger-Ellison syndrome and is very well tolerated.

The maximum pack size proposed (12 tablets) is small and equivalent only to 120 mg of drug.

3.10.4 Potential for Abuse

There is no evidence that famotidine has significant potential for abuse. Animal studies have not revealed overt behavioural changes that would suggest abuse potential, and clinical trials have not reported an association between famotidine and euphoria. There were no reports of product abuse in the last PSUR.

3.10.5 Safety in Special Patient Groups

3.10.5.1 Use in the Elderly

In clinical studies with ranitidine and famotidine in the elderly, efficacy and adverse events do not appear different to those in younger subjects. No dosage adjustment or particular precautions for elderly subjects are necessary from a pharmacological perspective. However, since the prevalence of some serious gastrointestinal disorders (particularly gastric cancer) rises considerably with rising age, special wording to alert these subjects to warning symptoms and signs is included in proposed patient information.

3.10.5.2 Use in Pregnancy

Heartburn and acid reflux are common in established pregnancy, principally because of changes in circulating hormones which lead to relaxation of the lower oesophageal sphincter. However, self-medication with H_2 receptor antagonists in pregnancy is not proposed, since the risks and benefits of any treatment in pregnancy should be explored by the patient and her physician.

Standard tests do not suggest teratogenic potential for either ranitidine or famotidine. Additionally, recorded usage in pregnancy for both drugs, although limited in amount, does not suggest an adverse impact on outcome. Should an unknowingly pregnant woman self-medicate with low dose famotidine or ranitidine inadvertently, these data provide considerable reassurance.

There are eight reports in the adverse event database for non-prescription famotidine of product use during pregnancy, but none of adverse outcome.

3.10.5.3 Use in Lactating Women

Famotidine can both be detected in the milk of lactating women after oral doses and thus feeding infants may be exposed to the drug. Therefore breast-feeding women should not self-medicate with famotidine without medical advice.

3.10.5.4 Use in Children

Heartburn and symptoms of acid reflux are unusual in young children and should therefore be investigated. A lower age limit of 16 years is proposed famotidine.

3.10.5.5 Renal Impairment

Famotidine is actively secreted by the renal tubules and elimination is primarily by the renal route for both drugs. In very severe renal impairment, elimination half-life may be prolonged. Although this is unlikely to lead to adverse consequences, patients with known renal impairment will be directed to take advice before self-medicating with famotidine.

3.10.5.6 Hepatic Impairment

Famotidine is metabolised to some degree in the liver. Therefore, on theoretical grounds, half-life may be prolonged in severe liver impairment, although this has not been observed in studies of such patients. Patients with known hepatic impairment will be advised to consult their physician before embarking on self-medication with famotidine.

3.11 SUMMARY OF OVERALL RISK/BENEFIT FOR SELF MEDICATION WITH THE H_2 RECEPTOR ANTAGONISTS

3.11.1 Benefits

The H_2 receptor antagonists, by inhibiting the secretion of gastric acid rather than neutralising acid after secretion, bring a new pharmacological approach to the self-medication of heartburn and acid-reflux. This new mode of action confers some important potential benefits over existing antacids. In particular the effect that low doses of famotidine (10 mg) and ranitidine (75 mg) have in reducing gastric acidity extends up to 12 hours resulting in prolonged duration of effect against acid related symptoms. Because antacids can only work while they reside in the stomach, these effects could not be reproduced with neutralising agents.

Studies with both drugs in low doses have confirmed efficacy in treating intermittent heartburn despite being made difficult by high placebo responses.

3.11.2 Risks

The H_2 receptor antagonists in prescription doses have been amongst the most widely used medicines world-wide and both extensive post-marketing surveillance and spontaneous reporting confirm that they have excellent safety profiles. Among the H_2 receptor antagonists famotidine and ranitidine have particular properties that make them suitable for self-medication in that, unlike cimetidine, they share:

- a lack of significant drug interactions
- excellent safety profiles including a lack of effect on circulating sex hormones and androgen receptors
- a lack of central nervous system effects in the elderly

The risk of self-medication for heartburn and acid reflux masking more serious disease is not unique to the H_2 receptor antagonists, since existing treatments can also produce temporary relief of symptoms caused by other conditions. The risks for each of the possible underlying diseases have been reviewed; the most important of these is arguably gastrointestinal malignancy because, although it is rare, this condition has a high mortality which may be positively influenced by early diagnosis.

Early diagnosis of gastric malignancy depends on the symptomatic presentation of the disease. Unfortunately, most gastric malignancies present when the tumour is advanced. Even delays in diagnosis of several months do not seem to influence stage of disease on presentation and therefore potential outcome. Patient education on the warning signs of gastric malignancy is important since these are often present on presentation but are not currently communicated to the population self-medicating for acid-related dyspepsia.

The proposed labels for famotidine include specific warnings on the symptoms which might indicate more serious underlying disease. The increased awareness of these symptoms is desirable, and may even improve consultation rates among appropriate patients. However, if patients deliberately choose to ignore these warnings, then they are at least not more likely to self-medicate inappropriately than at present.

3.12 CONCLUSION

The H_2 receptor antagonists have had unprecedented levels of usage world-wide and continue to be one of the best tolerated classes of medicines known. Ranitidine and famotidine have a notable lack of drug interactions and extremely well characterised safety profiles which are superior to many medicines which are currently available for self-medication.

The risk of masking more serious gastrointestinal disease has been extensively discussed in this document. Although this risk is logically no greater than with antacids, the proposed leaflet for famotidine contains adequate advice for consumers on the warning signs for serious disease. Where the H_2 receptor antagonists have been switched to self-medication status and have been commercially successful there has been no apparent impact on the pattern of consultation for upper gastrointestinal disease. In particular, experience in the USA where patients are able to self select, the introduction of the H_2 antagonists has expanded the self medication market but has not apparently diverted patients from consulting their physician.

The efficacy data in single episodes of heartburn and acid reflux for these drugs in low doses is at least as good as with antacids; and their long duration of effect on gastric acid secretion offers new benefits to the consumer suffering from simple heartburn.

The risk to benefit analysis for famotidine at the dose range proposed therefore appears very favourable and justifies the change in status for the proposed indications from P to GSL.

References

Note: copies of these references are provided in Appendix 10

1 Jones R, Lydeard S
Prevalence of symptoms of dyspepsia in the community. Br Med J; Jan 1989; 298: 30-32

2 Colin-Jones D G
Management of dyspepsia: report of a working party. The Lancet; Mar 1988; 576-579

3 Smith J L
Clinical Pharmacology of Famotidine. Digestion, 1985; 32, suppl 1; 15-23

4 Lebert P A, MacLeod S M, Mahon W A et al
Ranitidine kinetics and dynamics. Clin. Pharmacol. Ther. 1981; 30, 539-544.

5 Grimley C E, West J M, Loft D E et al
Early and late effects of low-dose famotidine, ranitidine or placebo on pentagastrin-stimulated gastric acid secretion in man. Aliment Pharmacol Ther. 1996; 10: 743-747

6 Grimley C, Cottrell J, Mann S G et al
Nocturnal intragastric acidity after over-the counter doses of famotidine, ranitidine or placebo. Aliment Pharmacol Ther. 1997; 11: 881-885

7 Howden C W
The Clinical Pharmacology of Famotidine. Rev. Contemp. Pharmacother 1992; 3: 377-388

8 Roberts C J C
Clinical Pharmacokinetics of Ranitidine. Clinical Pharmacokinetics; 1984; 9: 211-221

9 Vinçon G, Baldit C, Couzigou P et al
Pharmacokinetics of famotidine in patients with cirrhosis and ascites. Eur J Clin Pharmacol 1992; 43: 559-562

10 Lasseter K C
A double-blind, 9 period, placebo controlled, crossover study to investigate the effects of varying strengths of antacids on the pharmacodynamics of flavoured famotidine powder 10.0 and 20.0 mg
MSD Clinical Study Report MK-208, 1991

11 Simon T J, Berlin R G, Gardner A H et al
Self-directed treatment of intermittent heartburn; a randomized, multicenter, double-blind, placebo-controlled evaluation of antacid and low doses of an H_2 -receptor antagonist (famotidine). American Journal of Therapeutics 1995; 2: 304-313.

12 Mann S G, Murakami A, McCarroll K et al
Low dose famotidine in the prevention of sleep disturbance caused by heartburn after an evening meal. Aliment Pharmacol Ther; 1995; 9: 395-401

13 Mann S G, Cottrell J, Murakami A et al
Prevention of heartburn relapse by low-dose famotidine: a test meal model for duration of symptom control. Aliment Pharmacol Ther; 1997; 11: 121-127

14 Thompson W G and Heaton K W
Heartburn and globus in apparently healthy people. CMA Journal; 1982; 126: 46-48

15 Nebel O T, Fornes M F, and Castell D O
Symptomatic Gastroesophageal Reflux: Incidence and Precipitating Factors. Digestive Diseases, 1976; 21: 953-956

16 Richter J E
Heartburn, Dysphagia, Odynophagia, and other Esophageal Symptoms. In Sleisenger et al (ed) Gastrointestinal Disease 1993 5th Ed; 1: 331-340

17 Babka J C and Castell D O
On the Genesis of Heartburn. The Effects of Specific Foods on the Lower Esophageal Sphincter. Digestive Diseases, 1973; 18: 391-397

18 Bennett J R
Heartburn and Gastro-oesophageal Reflux. BJCP, 1991; 45: 273-277

19 Korn S H, Vassil T C, Raskin S J et al
Usage trial of famotidine
Gastroenterology, 1995; 108 A135

20 Pepcid User Study. Market Research commisioned by Pharmacia. December 1995

21 Holt S
Over-the-Counter Histamine H^2-Receptor Antagonists. How will they effect Treatment of Acid-Related Diseases? Drugs, 1994; 47, 1-11

22 Schiller L R, Fordtran J S
Ulcer complications during short term therapy of duodenal ulcer with active agents and placebo. Gasterenterology 1986; 90: 478-481.

23 Weinbeck W and Barnert J
Epidemiology of Reflux Disease and Reflux Esophagitis. Scand J Gastroenterol 1989, 24 (Suppl 156): 7-13.

24 Colin-Jones D G
Dyspepsia Update. Scand J Gastroenterol 1995; 30 Suppl 210: 32-35

25 Hallissey M T, Allum W H, Jewkes A J et al
Early detection of gastric cancer. Br Med J 1990; 301: 513-515

26 Martin I G, Young S, Sue-Ling H et al
Delays in the diagnosis of oesophagogastric cancer: a consecutive case series. British Med J; 1997; 314: 467-470

27 Colin-Jones D G, Langman M J S, Lawson D H et al
Postmarketing Surveillane of Safety of Cimetidine: 10 Year Mortality Report. Gut 1992; 33: 1280-1284

28 Haugstvedt T K, Viste A, Eide G E et al
Patient and Physician Treatment Delay in Patients with Stomach Cancer in Norway: Is It Important? Scand J Gastroenterol 1991; 26: 611-619.

29 Allum W H, Powell D J, McConkey C C et al
Gastric cancer: a 25 year review. Br. J Surg. 1989; 76: 535-540

30 Siewert J R and Fink U
Commentary: Britain does better than Germany before patients reach hospital. British Med J; 1997; 314: 471

31 Christie J, Shepherd N A, Codling B W, Valori R M
Gastric cancer below the age of 55: implications for screening patients with uncomplicated dyspepsia. Gut 1997; 41:513-517

32 Anderson M and Schou J S
Adverse Reactions to H_2 - Receptor Antagonists in Denmark Before and After Transfer of Cimetidine and Ranitidine to Over-the-counter Status. Pharmacology & Toxicology 1991; 69: 253-258

33 Andersen M and Schou J S
Safety Implications of the Over-the Counter Availability of H_2-Antagonists. Drug Safety 1993; 8, 179-185

34 Oster G, Huse D M, Delea T E et al
The Risks and Benefits of an Rx-to-OTC Switch. The Case of Over-the-Counter H_2 - Blockers. Medical Care 1990; 28: 834-852

35 Martin R M, Lim A G, Kerry S M, Hilton S R
Trends in prescribing H_2 receptor antagonists and proton pump inhibitors in primary care.
Aliment Pharmacol Ther 1998; 12: 797-805

36 Levitt M D
Review article: Lack of clinical significance of the interaction between H_2-receptor antagonists and ethanol. Aliment Pharmacol Ther 1993; 7: 131-138

Annex 2

APPENDIX 1

PRESENT SUMMARIES OF PRODUCT CHARACTERISTICS

- Pepcid AC
- Pepcid AC Chewable

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF MEDICINAL PRODUCT

Pepcid®AC (when distributed by Johnson & Johnson.MSD Consumer Pharmaceuticals)

Boots Excess Acid Control (when distributed by The Boots Company Plc)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Famotidine USP 10 mg

3 PHARMACEUTICAL FORM

Film-coated tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The short-term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity.

Prevention of these symptoms when associated with food and beverage (drink) including nocturnal symptoms associated with the evening meal and expected to cause sleep disturbance.

A patient information leaflet will be inside or attached to the packs for this product.

4.2 Posology and method of administration

Adults and children 16 years of age or older:

Dosage: 10 mg

Dosage interval :

One tablet (10 mg) for symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity.

or

One tablet (10 mg) taken 15 minutes before consuming food and beverage (drink) known to be associated with or to provoke these symptoms. When these symptoms are expected to interfere with sleep, one tablet (10 mg) taken one hour before the evening meal.

Maximum intake in 24 hours : two tablets (20 mg)

Patients must seek medical advice:
- if symptoms fail to respond,
- if symptoms recur following self treatment with Pepcid AC,
- if symptoms persist after 2 weeks treatment.

The maximum treatment period is two weeks

No dosage adjustment is necessary for the elderly

Pepcid AC is not recommended for use in children less than 16 years of age.

4.3 Contra-indications

Hypersensitivity to any component of this product

Pepcid AC is not indicated in the following patient groups unless advised by their physician:

Patients with moderate or severe renal failure.
Patients with severe hepatic impairment.
Patients suffering from any other illness or taking any medications either physician-prescribed or self-prescribed.

Patients who are middle aged or older with new or recently changed dyspeptic symptoms.
Patients with unintended weight loss in association with dyspeptic symptoms.

4.4 Special warnings and special precautions for use

In clinical trials, patients with other underlying acid related gastro-intestinal diseases (eg duodenal ulcer, gastric ulcer) did not experience complications; in general, they did not exhibit a clinically significant deterioration in their condition.

If patients have difficulty swallowing, or abdominal discomfort persists they should seek medical advice.

4.5 Interactions with other medicaments and other forms of interaction

No drug interactions of clinical importance have been identified. Pepcid AC does not interact with the cytochrome P450-linked drug metabolising enzyme system. Compounds metabolised by this system which have been tested in man have included warfarin, theophylline, phenytoin, diazepam, propranolol, aminopyrine and antipyrine. Famotidine does not appear to affect the disposition of these drugs when they are taken orally.

Concomitant use of aluminium hydroxide/magnesium hydroxide at the usual doses does not influence the pharmacodynamics or bioavailability of Pepcid AC.

Famotidine does not affect blood alcohol levels following oral ingestion of ethanol.

4.6 Pregnancy and lactation

Pepcid AC is not recommended for use in pregnancy. Before a decision is made to use Pepcid AC during pregnancy, the physician should weigh the potential benefits from the drug against the possible risks involved.

Famotidine is secreted in human milk; therefore breast-feeding mothers should either stop breast-feeding or not take the drug.

4.7 Effects on ability to drive and operate machinery

In clinical trials with famotidine, there has been no observed impairment of the ability to drive or operate machinery.

4.8 Undesirable effects

Famotidine has been shown to be generally well tolerated. In clinical trials for the OTC indications side effects reported as possibly/probably or definitely drug related and occurring in ≥ 1% of patients were headache and dizziness. These occurred with comparable frequency in patients treated with placebo.

Other side effects reported even less frequently included dry mouth, nausea and/or vomiting, constipation, diarrhoea, abdominal discomfort or distension, anorexia, fatigue, rash, pruritus, and urticaria, liver enzyme abnormalities, cholestatic jaundice, anaphylaxis, angioedema, arthralgia. Pancytopenia, leucopenia, and isolated cases of worsening of existing hepatic disease have been reported; however, a causal relationship to therapy with famotidine has not been established. No clinically significant increase in endocrine or gonadal function has been reported. Gynaecomastia has been reported rarely. In most cases that were followed up, it was reversible on discontinuing treatment.

4.9 Overdose

There is no experience to date with overdosage.
The usual measures to remove unabsorbed material from the gastro-intestinal tract, clinical monitoring and supportive therapy should be employed.
Patients with Zollinger-Ellison syndrome have tolerated doses up to 800 mg/day for more than a year without development of significant adverse effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pepcid AC is a potent competitive H_2-receptor antagonist. At the recommended doses, Pepcid AC has a long duration of action and is highly effective at relatively low blood concentrations. Duration of action, plasma concentration and urinary recovery are dose related.

Pepcid AC reduces the acid and pepsin content, as well as the volume of basal, nocturnal and stimulated gastric secretion.

In clinical trials, Pepcid AC provided effective symptom relief. When administered 15 minutes before a test meal, famotidine reduced symptoms that would otherwise have been expected. Administration of famotidine before an evening meal prevented nocturnal acid-related symptoms and therefore prevented symptom-related interference with sleep.

After oral administration a dose-response relationship was clearly demonstrated from 0.5 to 10 mg famotidine in terms of raising gastric pH between and after meals. Famotidine doses of 2.5 to 10 mg were demonstrated to produce a statistically significant effect on gastric pH as compared to placebo. The onset of effect for the 5 and 10 mg doses was seen at approximately 1.5 hours post-dose, while that of the 2.5 mg dose was not seen until 2.5 hours post-dose. The maximum effect, as measured by peak mean pH value, occurred at 3.5 hours. The activity of the 5 and 10 mg doses continued until approximately 9 hours post-dose in daytime studies. Additionally, a nighttime study demonstrated that famotidine 10mg statistically significantly increased gastric pH for 12 hours post-dose as compared to placebo. Famotidine is well tolerated at these dose levels.

Systemic effects of famotidine in the CNS, cardiovascular, respiratory or endocrine systems were not noted in clinical pharmacology studies. Also, no anti-androgenic effects were noted in clinical pharmacology studies.

5.2 Pharmacokinetic properties

Pepcid AC obeys linear kinetics.

Compared to historical data from younger subjects, age does not appear to affect the bioavailability of single doses of famotidine. However, the elimination appears to be reduced in elderly subjects compared with younger subjects, possibly due to age related reductions in renal function.

Famotidine exhibits dose-related peak plasma concentrations occurring at 1-3 hours. The mean bioavailability of an oral dose is 40-45%. Bioavailability is not clinically affected by the presence of food in the stomach. Famotidine undergoes minimal first-pass metabolism. Repeated doses do not lead to accumulation of the drug.

Protein binding in the plasma is relatively low (15-20%). The plasma half-life after a single oral dose or multiple repeated doses (for five days) was approximately three hours. Metabolism of the drug occurs in the liver, with formation of the inactive sulphoxide metabolite.

Following oral administration, the mean urinary excretion of the absorbed dose of famotidine is 65-70%. Of the total oral dose administered, 25-30% is recovered as unchanged compound in the urine. Renal clearance is 250-450 ml/min, indicating some tubular excretion. A small amount may be excreted as the sulphoxide.

5.3 Preclinical safety data

Extensive preclinical safety studies have been performed in dogs, rats, mice and rabbits using oral and intravenous routes of administration of famotidine. Minimal toxicological effects (after acute, subacute or chronic administration) have been observed, even at extremely high dosage levels and for extended periods of administration.

No evidence of teratogenic, mutagenic or carcinogenic effects or alteration of reproductive function have been seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylcellulose Ph Eur, Magnesium Stearate Ph Eur, Hydroxypropyl Methylcellulose Ph Eur, Microcrystalline Cellulose Ph Eur, Pregelatinised Maize Starch BP, Red Iron Oxide E172, Talc Ph Eur, Titanium Dioxide E171 Ph Eur, Carnauba Wax Ph Eur.

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at temperatures below 30°C
Protect from moisture
Protect from light

Keep out of the reach of children

6.5 Nature and contents of container

Blister packs with PVC/PE/PVDC base and aluminium foil lidding

The packs will contain:
Blister packs of 2, 6, 10, 12, 18 and 20 tablets

6.6 Instructions for use/handling

Instructions for use will appear on the packaging and in the patient package leaflet. No special handling precautions.

7 MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road
Hoddesdon
HERTS
EN11 9BU

Pepcid AC distributed by :

Johnson & Johnson o MSD
Consumer Pharmaceuticals
Enterprise House
Station Road, Loudwater,
High Wycombe
Buckinghamshire HP10 9UF

Boots Excess Acid Control distributed by:

The Boots Company Plc

1 Thane Road West
Beeston
Nottingham
NG2 3AA

8 MARKETING AUTHORISATION NUMBER

PL 0025/0312

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

4 February 1994/26 March 1999

10 DATE OF (PARTIAL) REVISION OF THE TEXT

July 1999

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF MEDICINAL PRODUCT

Pepcid® AC Chewable

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Famotidine 10 mg

3 PHARMACEUTICAL FORM

Chewable tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The short-term symptomatic relief of heartburn, indigestion, acid indigestion, dyspepsia and hyperacidity.

Prevention of these symptoms when associated with food and beverage (drink) including nocturnal symptoms associated with the evening meal and expected to cause sleep disturbance.

A patient information leaflet will be inside or attached to the packs for this product.

4.2 Posology and method of administration

Adults and children 16 years of age or older:

Dosage : 10 mg

Dosage interval :
One tablet (10 mg) to be chewed for symptomatic relief of heartburn, indigestion, acid indigestion, dyspepsia and hyperacidity

or

One tablet (10 mg) to be chewed 15 minutes before consuming food and beverage (drink) known to be associated with or to provoke these symptoms. When these symptoms are expected to interfere with sleep, one tablet (10 mg) to be chewed one hour before the evening meal.

Maximum intake in 24 hours : two tablets (20 mg)

Patients must seek medical advice:
- if symptoms fail to respond,
- if symptoms recur following self treatment with Pepcid AC Chewable tablets,
- if symptoms persist after two weeks treatment.

The maximum treatment period is 2 weeks.

No dosage adjustment is necessary for the elderly.

Pepcid AC Chewable is not recommended for use in children less than 16 years of age.

4.3 Contra-indications

Hypersensitivity to any component of this product.

Pepcid AC Chewable is not indicated in the following patient groups unless advised by their physician:

Patients with moderate or severe renal failure.
Patients with severe hepatic impairment.

Patients suffering from any other illness or taking any medications either physician- prescribed or self-prescribed.

Patients who are middle aged or older with new or recently changed dyspeptic symptoms.
Patients with unintended weight loss in association with dyspeptic symptoms.

4.4 Special warnings and special precautions for use

In clinical trials, patients with other underlying acid related gastro-intestinal diseases (eg duodenal ulcer, gastric ulcer) did not experience complications; in general, they did not exhibit a clinically significant deterioration in their condition.

If patients have difficulty swallowing, or abdominal discomfort persists they should seek medical advice.

4.5 Interactions with other medicaments and other forms of interaction

No drug interactions of clinical importance have been identified. Pepcid AC Chewable does not interact with the cytochrome P450-linked drug metabolising enzyme system. Compounds metabolised by this system which have been tested in man have included warfarin, theophylline, phenytoin, diazepam, propranolol, aminopyrine and antipyrine. Famotidine does not appear to affect the disposition of these drugs when they are taken orally.

Concomitant use of aluminium hydroxide/magnesium hydroxide at the usual doses does not influence the pharmacodynamics or bioavailability of Pepcid AC Chewable.

Famotidine does not affect blood alcohol levels following oral ingestion of ethanol.

4.6 Pregnancy and lactation

Pepcid AC Chewable is not recommended for use in pregnancy. Before a decision is made to use Pepcid AC Chewable during pregnancy, the physician should weigh the potential benefits from the drug against the possible risks involved.

Famotidine is secreted in human milk; therefore breast-feeding mothers should either stop breast-feeding or not take the drug.

4.7 Effects on ability to drive and operate machinery

In clinical trials with famotidine, there has been no observed impairment of the ability to drive or operate machinery.

4.8 Undesirable effects

Famotidine has been shown to be generally well tolerated. In clinical trials for the OTC indications side effects reported as possibly/probably or definitely drug related and occurring in ≥ 1% of patients were headache and dizziness. These occurred with comparable frequency in patients treated with placebo.

Other side effects reported even less frequently included dry mouth, nausea and/or vomiting, constipation, diarrhoea, abdominal discomfort or distension, anorexia, fatigue, rash, pruritus, and urticaria, liver enzyme abnormalities, cholestatic jaundice, anaphylaxis, angioedema, arthralgia. Pancytopenia, leucopenia, and isolated cases of worsening of existing hepatic disease have been reported. However, a causal relationship to therapy with famotidine has not been established. No clinically significant increase in endocrine or gonadal function has been reported. Gynaecomastia has been reported rarely. In most cases that were followed up, it was reversible on discontinuing treatment.

4.9 Overdose

There is no experience to date with overdosage. The usual measures to remove unabsorbed material from the gastro-intestinal tract, clinical monitoring and supportive therapy should be employed. Patients with Zollinger-Ellison syndrome have tolerated doses up to 800 mg/day for more than a year without development of significant adverse effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pepcid AC Chewable is a potent competitive H_2-receptor antagonist. At the recommended doses, Pepcid AC Chewable has a long duration of action and is highly effective at relatively low blood concentrations. Duration of action, plasma concentration and urinary recovery are dose related.

Pepcid AC Chewable reduces the acid and pepsin content, as well as the volume of basal, nocturnal and stimulated gastric secretion.

In clinical trials, Pepcid AC Chewable provided effective symptom relief. When administered 15 minutes before a test meal, famotidine reduced symptoms that would otherwise have been expected. Administration of famotidine before an evening meal prevented nocturnal acid-related symptoms and therefore prevented symptom-related interference with sleep.

After oral administration a dose-response relationship was clearly demonstrated from 0.5 to 10 mg famotidine in terms of raising gastric pH between and after meals. Famotidine doses of 2.5 to 10 mg were demonstrated to produce a statistically significant effect on gastric pH as compared to placebo. The onset of effect for the 5 and 10 mg doses was seen at approximately 1.5 hours post-dose, while that of the 2.5 mg dose was not seen until 2.5 hours post-dose. The maximum effect, as measured by peak mean pH value, occurred at 3.5 hours. The activity of the 5 and 10 mg doses continued until approximately 9 hours post-dose in daytime studies. Additionally, a night-time study demonstrated that famotidine 10mg statistically significantly increased gastric pH for 12 hours post-dose as compared to placebo. Famotidine is well tolerated at these dose levels.

Systemic effects of famotidine in the CNS, cardiovascular, respiratory or endocrine systems were not noted in clinical pharmacology studies. Also, no anti-androgenic effects were noted in clinical pharmacology studies.

5.2 Pharmacokinetic properties

Pepcid AC Chewable obeys linear kinetics.

Compared to historical data from younger subjects, age does not appear to affect the bioavailability of single doses of famotidine. However, the elimination appears to be reduced in elderly subjects compared with younger subjects, possibly due to age related reductions in renal function.

Famotidine exhibits dose-related peak plasma concentrations occurring at 1-3 hours. The mean bioavailability of an oral dose is 40-45%. Bioavailability is not clinically affected by the presence of food in the stomach. Famotidine undergoes minimal first-pass metabolism. Repeated doses do not lead to accumulation of the drug.

Protein binding in the plasma is relatively low (15-20%). The plasma half-life after a single oral dose or multiple repeated doses (for five days) was approximately three hours.

Metabolism of the drug occurs in the liver, with formation of the inactive sulphoxide metabolite.

Following oral administration, the mean urinary excretion of the absorbed dose of famotidine is 65-70%. Of the total oral dose administered, 25-30% is recovered as unchanged compound in the urine. Renal clearance is 250-450 ml/min, indicating some tubular excretion. A small amount may be excreted as the sulphoxide.

A 10 mg chewable tablet has been shown to be bioequivalent to a 10 mg film coated tablet.

5.3 Preclinical safety data

Extensive preclinical safety studies have been performed in dogs, rats, mice and rabbits using oral and intravenous routes of administration of famotidine. Minimal toxicological effects (after acute, subacute or chronic administration) have been observed, even at extremely high dosage levels and for extended periods of administration.

No evidence of teratogenic, mutagenic or carcinogenic effects or alteration of reproductive function have been seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylcellulose Ph Eur, Magnesium Stearate Ph Eur, Lactose Ph Eur, Cellulose Acetate NF, Aspartame NF, Mannitol Ph Eur, Hydroxypropyl Methylcellulose Ph Eur, Microcrystalline Cellulose Ph Eur, Red Iron Oxide (E172), Prosweet Powder, Trusil Natural Peppermint.

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at temperatures below 30° C
Protect from moisture

Keep out of the reach of children

6.5 Nature and contents of container

Strip packs composed of Paper/LDPE/Aluminium foil

The packs will contain : 2, 6, 8, 10, 12, 18 and 20 tablets

6.6 Instructions for use/handling

Instructions for use will appear on the packaging and in the patient package leaflet.
No special handling precautions.

7 PRODUCT LICENCE HOLDER

Merck, Sharp & Dohme Limited
Hertford Road
Hoddesdon
HERTS
EN11 9BU

Distributed by :

Johnson & Johnson . MSD
Consumer Pharmaceuticals
Enterprise House
Station Road
Loudwater
High Wycombe
BUCKS HP10 9UF

Tel : 01494 450778

8 MARKETING AUTHORISATION NUMBER

PL 00025/0313

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

2 April 1996

10 DATE OF (PARTIAL) REVISION OF THE TEXT

22 October 1997

Annex 3

APPENDIX 2

PROPOSED SUMMARIES OF PRODUCT CHARACTERISTICS

- Pepcid AC
- Pepcid AC Chewable

Proposed changes are boxed

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF MEDICINAL PRODUCT

Pepcid® AC (when distributed by Johnson & Johnson.MSD Consumer Pharmaceuticals)

Boots Excess Acid Control (when distributed by The Boots Company Plc)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Famotidine USP 10 mg

3 PHARMACEUTICAL FORM

Film-coated tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

P Indications

The short-term symptomatic relf of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity.

Prevention of these symptoms when associated with food and beverage (drink) including nocturnal symptoms associate with the evening meal and expected to cause sleep disturbance.

GSL Indications:

The short-term symptomatic relf of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity.

A patient information leaflet will be inside or attached to the packs for this product.

4.2 Posology and method of administration

Adults and children 16 years of age or older:

Dosage: 10 mg

Dosage interval :

One tablet (10 mg) for symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity.

In addition, for P use only:

One tablet (10 mg) taken 15 minutes before consuming food and beverage (drink) known to be associated with or to provoke these symptoms. When these symptoms are expected to interfere with sleep, one tablet (10 mg) taken one hour before the evening meal.

Maximum intake in 24 hours : two tablets (20 mg)

Patients must seek medical advice:
- if symptoms fail to respond,
- if symptoms recur following self treatment with Pepcid AC,
- if symptoms persist after 2 weeks treatment.

The maximum treatment period is two weeks

No dosage adjustment is necessary for the elderly

Pepcid AC is not recommended for use in children less than 16 years of age.

4.3 Contra-indications

Hypersensitivity to any component of this product

Pepcid AC is not indicated in the following patient groups unless advised by their physician:

Patients with moderate or severe renal failure.
Patients with severe hepatic impairment.
Patients suffering from any other illness or taking any medications either physician-prescribed or self-prescribed.

Patients who are middle aged or older with new or recently changed dyspeptic symptoms.
Patients with unintended weight loss in association with dyspeptic symptoms.

4.4 Special warnings and special precautions for use

In clinical trials, patients with other underlying acid related gastro-intestinal diseases (eg duodenal ulcer, gastric ulcer) did not experience complications; in general, they did not exhibit a clinically significant deterioration in their condition.

If patients have difficulty swallowing, or abdominal discomfort persists they should seek medical advice.

4.5 Interactions with other medicaments and other forms of interaction

No drug interactions of clinical importance have been identified. Pepcid AC does not interact with the cytochrome P450-linked drug metabolising enzyme system. Compounds metabolised by this system which have been tested in man have included warfarin, theophylline, phenytoin, diazepam, propranolol, aminopyrine and antipyrine. Famotidine does not appear to affect the disposition of these drugs when they are taken orally.

Concomitant use of aluminium hydroxide/magnesium hydroxide at the usual doses does not influence the pharmacodynamics or bioavailability of Pepcid AC.

Famotidine does not affect blood alcohol levels following oral ingestion of ethanol.

4.6 Pregnancy and lactation

Pepcid AC is not recommended for use in pregnancy. Before a decision is made to use Pepcid AC during pregnancy, the physician should weigh the potential benefits from the drug against the possible risks involved.

Famotidine is secreted in human milk; therefore breast-feeding mothers should either stop breast-feeding or not take the drug.

4.7 Effects on ability to drive and operate machinery

In clinical trials with famotidine, there has been no observed impairment of the ability to drive or operate machinery.

4.8 Undesirable effects

Famotidine has been shown to be generally well tolerated. In clinical trials for the OTC indications side effects reported as possibly/probably or definitely drug related and occurring in ≥ 1% of patients were headache and dizziness. These occurred with comparable frequency in patients treated with placebo.

Other side effects reported even less frequently included dry mouth, nausea and/or vomiting, constipation, diarrhoea, abdominal discomfort or distension, anorexia, fatigue, rash, pruritus, and urticaria, liver enzyme abnormalities, cholestatic jaundice, anaphylaxis, angioedema, arthralgia. Pancytopenia, leucopenia, and isolated cases of worsening of existing hepatic disease have been reported; however, a causal relationship to therapy with famotidine has not been established. No clinically significant increase in endocrine or gonadal function has been reported. Gynaecomastia has been reported rarely. In most cases that were followed up, it was reversible on discontinuing treatment.

4.9 Overdose

There is no experience to date with overdosage.
The usual measures to remove unabsorbed material from the gastro-intestinal tract, clinical monitoring and supportive therapy should be employed.
Patients with Zollinger-Ellison syndrome have tolerated doses up to 800 mg/day for more than a year without development of significant adverse effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pepcid AC is a potent competitive H_2-receptor antagonist. At the recommended doses, Pepcid AC has a long duration of action and is highly effective at relatively low blood concentrations. Duration of action, plasma concentration and urinary recovery are dose related.

Pepcid AC reduces the acid and pepsin content, as well as the volume of basal, nocturnal and stimulated gastric secretion.

In clinical trials, Pepcid AC provided effective symptom relief. When administered 15 minutes before a test meal, famotidine reduced symptoms that would otherwise have been expected. Administration of famotidine before an evening meal prevented nocturnal acid-related symptoms and therefore prevented symptom-related interference with sleep.

After oral administration a dose-response relationship was clearly demonstrated from 0.5 to 10 mg famotidine in terms of raising gastric pH between and after meals. Famotidine doses of 2.5 to 10 mg were demonstrated to produce a statistically significant effect on gastric pH as compared to placebo. The onset of effect for the 5 and 10 mg doses was seen at approximately 1.5 hours post-dose, while that of the 2.5 mg dose was not seen until 2.5 hours post-dose. The maximum effect, as measured by peak mean pH value, occurred at 3.5 hours. The activity of the 5 and 10 mg doses continued until approximately 9 hours post-dose in daytime studies. Additionally, a nighttime study demonstrated that famotidine 10mg statistically significantly increased gastric pH for 12 hours post-dose as compared to placebo. Famotidine is well tolerated at these dose levels.

Systemic effects of famotidine in the CNS, cardiovascular, respiratory or endocrine systems were not noted in clinical pharmacology studies. Also, no anti-androgenic effects were noted in clinical pharmacology studies.

5.2 Pharmacokinetic properties

Pepcid AC obeys linear kinetics.

Compared to historical data from younger subjects, age does not appear to affect the bioavailability of single doses of famotidine. However, the elimination appears to be reduced in elderly subjects compared with younger subjects, possibly due to age related reductions in renal function.

Famotidine exhibits dose-related peak plasma concentrations occurring at 1-3 hours. The mean bioavailability of an oral dose is 40-45%. Bioavailability is not clinically affected by the presence of food in the stomach. Famotidine undergoes minimal first-pass metabolism. Repeated doses do not lead to accumulation of the drug.

Protein binding in the plasma is relatively low (15-20%). The plasma half-life after a single oral dose or multiple repeated doses (for five days) was approximately three hours. Metabolism of the drug occurs in the liver, with formation of the inactive sulphoxide metabolite.

Following oral administration, the mean urinary excretion of the absorbed dose of famotidine is 65-70%. Of the total oral dose administered, 25-30% is recovered as unchanged compound in the urine. Renal clearance is 250-450 ml/min, indicating some tubular excretion. A small amount may be excreted as the sulphoxide.

5.3 Preclinical safety data

Extensive preclinical safety studies have been performed in dogs, rats, mice and rabbits using oral and intravenous routes of administration of famotidine. Minimal toxicological effects (after acute, subacute or chronic administration) have been observed, even at extremely high dosage levels and for extended periods of administration.

No evidence of teratogenic, mutagenic or carcinogenic effects or alteration of reproductive function have been seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylcellulose Ph Eur, Magnesium Stearate Ph Eur, Hydroxypropyl Methylcellulose Ph Eur, Microcrystalline Cellulose Ph Eur, Pregelatinised Maize Starch BP, Red Iron Oxide E172, Talc Ph Eur, Titanium Dioxide E171 Ph Eur, Carnauba Wax Ph Eur.

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at temperatures below 30°C
Protect from moisture
Protect from light

Keep out of the reach of children

6.5 Nature and contents of container

Blister packs with PVC/PE/PVDC base and aluminium foil lidding

For P use
The packs will contain:
Blister packs of 2, 6, 10, 12, 18 and 20 tablets

For GSL use, the packs will contain:
Blister packs of 2, 6, 10 and 12 tablets

6.6 Instructions for use/handling

Instructions for use will appear on the packaging and in the patient package leaflet. No special handling precautions.

7 MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road
Hoddesdon
HERTS
EN11 9BU

Pepcid AC distributed by : [redacted] Excess Acid Control distributed by:

Johnson & Johnson o MSD
Consumer Pharmaceuticals
Enterprise House
Station Road, Loudwater,
High Wycombe
Buckinghamshire HP10 9UF

[redacted]

[redacted]

8 MARKETING AUTHORISATION NUMBER

PL 0025/0312

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

4 February 1994/26 March 1999

10 DATE OF (PARTIAL) REVISION OF THE TEXT

27.09.99

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF MEDICINAL PRODUCT

Pepcid® AC Chewable

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Famotidine 10 mg

3 PHARMACEUTICAL FORM

Chewable tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

P Indications:

The short-term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity.

Prevention of these symptoms when associated with food and beverage (drink) including nocturnal symptoms associated with the evening meal and expected to cause sleep disturbance.

GSL Indications:

The short-term symptomatic relief of heartburn, indigestion, acid indigestion dyspepsia and hyperacidity.

4.2 Posology and method of administration

Adults and children 16 years of age or older:

Dosage : 10 mg

Dosage interval :
One tablet (10 mg) to be chewed for symptomatic relief of heartburn, indigestion, acid indigestion, dyspepsia and hyperacidity

In addition, for P use only

One tablet (10 mg) to be chewed 15 minutes before consuming food and beverage (drink) known to be associated with or to provoke these symptoms. When these symptoms are expected to interfere with sleep, one tablet (10 mg) to be chewed one hour before the evening meal.

Maximum intake in 24 hours : two tablets (20 mg)

Patients must seek medical advice:
- if symptoms fail to respond,
- if symptoms recur following self treatment with Pepcid AC Chewable tablets,
- if symptoms persist after two weeks treatment.

The maximum treatment period is 2 weeks.

No dosage adjustment is necessary for the elderly.

Pepcid AC Chewable is not recommended for use in children less than 16 years of age.

4.3 Contra-indications

Hypersensitivity to any component of this product.

Pepcid AC Chewable is not indicated in the following patient groups unless advised by their physician:

Patients with moderate or severe renal failure.
Patients with severe hepatic impairment.

Patients suffering from any other illness or taking any medications either physician- prescribed or self-prescribed.

Patients who are middle aged or older with new or recently changed dyspeptic symptoms.
Patients with unintended weight loss in association with dyspeptic symptoms.

4.4 Special warnings and special precautions for use

In clinical trials, patients with other underlying acid related gastro-intestinal diseases (eg duodenal ulcer, gastric ulcer) did not experience complications; in general, they did not exhibit a clinically significant deterioration in their condition.

If patients have difficulty swallowing, or abdominal discomfort persists they should seek medical advice.

4.5 Interactions with other medicaments and other forms of interaction

No drug interactions of clinical importance have been identified. Pepcid AC Chewable does not interact with the cytochrome P450-linked drug metabolising enzyme system. Compounds metabolised by this system which have been tested in man have included warfarin, theophylline, phenytoin, diazepam, propranolol, aminopyrine and antipyrine. Famotidine does not appear to affect the disposition of these drugs when they are taken orally.

Concomitant use of aluminium hydroxide/magnesium hydroxide at the usual doses does not influence the pharmacodynamics or bioavailability of Pepcid AC Chewable.

Famotidine does not affect blood alcohol levels following oral ingestion of ethanol.

4.6 Pregnancy and lactation

Pepcid AC Chewable is not recommended for use in pregnancy. Before a decision is made to use Pepcid AC Chewable during pregnancy, the physician should weigh the potential benefits from the drug against the possible risks involved.

Famotidine is secreted in human milk; therefore breast-feeding mothers should either stop breast-feeding or not take the drug.

4.7 Effects on ability to drive and operate machinery

In clinical trials with famotidine, there has been no observed impairment of the ability to drive or operate machinery.

4.8 Undesirable effects

Famotidine has been shown to be generally well tolerated. In clinical trials for the OTC indications side effects reported as possibly/probably or definitely drug related and occurring in ≥ 1% of patients were headache and dizziness. These occurred with comparable frequency in patients treated with placebo.

Other side effects reported even less frequently included dry mouth, nausea and/or vomiting, constipation, diarrhoea, abdominal discomfort or distension, anorexia, fatigue, rash, pruritus, and urticaria, liver enzyme abnormalities, cholestatic jaundice, anaphylaxis, angioedema, arthralgia. Pancytopenia, leucopenia, and isolated cases of worsening of existing hepatic disease have been reported. However, a causal relationship to therapy with famotidine has not been established. No clinically significant increase in endocrine or gonadal function has been reported. Gynaecomastia has been reported rarely. In most cases that were followed up, it was reversible on discontinuing treatment.

4.9 Overdose

There is no experience to date with overdosage. The usual measures to remove unabsorbed material from the gastro-intestinal tract, clinical monitoring and supportive therapy should be employed. Patients with Zollinger-Ellison syndrome have tolerated doses up to 800 mg/day for more than a year without development of significant adverse effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pepcid AC Chewable is a potent competitive H_2-receptor antagonist. At the recommended doses, Pepcid AC Chewable has a long duration of action and is highly effective at relatively low blood concentrations. Duration of action, plasma concentration and urinary recovery are dose related.

Pepcid AC Chewable reduces the acid and pepsin content, as well as the volume of basal, nocturnal and stimulated gastric secretion.

In clinical trials, Pepcid AC Chewable provided effective symptom relief. When administered 15 minutes before a test meal, famotidine reduced symptoms that would otherwise have been expected. Administration of famotidine before an evening meal prevented nocturnal acid-related symptoms and therefore prevented symptom-related interference with sleep.

After oral administration a dose-response relationship was clearly demonstrated from 0.5 to 10 mg famotidine in terms of raising gastric pH between and after meals. Famotidine doses of 2.5 to 10 mg were demonstrated to produce a statistically significant effect on gastric pH as compared to placebo. The onset of effect for the 5 and 10 mg doses was seen at approximately 1.5 hours post-dose, while that of the 2.5 mg dose was not seen until 2.5 hours post-dose. The maximum effect, as measured by peak mean pH value, occurred at 3.5 hours. The activity of the 5 and 10 mg doses continued until approximately 9 hours post-dose in daytime studies. Additionally, a night-time study demonstrated that famotidine 10mg statistically significantly increased gastric pH for 12 hours post-dose as compared to placebo. Famotidine is well tolerated at these dose levels.

Systemic effects of famotidine in the CNS, cardiovascular, respiratory or endocrine systems were not noted in clinical pharmacology studies. Also, no anti-androgenic effects were noted in clinical pharmacology studies.

5.2 Pharmacokinetic properties

Pepcid AC Chewable obeys linear kinetics.

Compared to historical data from younger subjects, age does not appear to affect the bioavailability of single doses of famotidine. However, the elimination appears to be reduced in elderly subjects compared with younger subjects, possibly due to age related reductions in renal function.

Famotidine exhibits dose-related peak plasma concentrations occurring at 1-3 hours. The mean bioavailability of an oral dose is 40-45%. Bioavailability is not clinically affected by the presence of food in the stomach. Famotidine undergoes minimal first-pass metabolism. Repeated doses do not lead to accumulation of the drug.

Protein binding in the plasma is relatively low (15-20%). The plasma half-life after a single oral dose or multiple repeated doses (for five days) was approximately three hours.

Metabolism of the drug occurs in the liver, with formation of the inactive sulphoxide metabolite.

Following oral administration, the mean urinary excretion of the absorbed dose of famotidine is 65-70%. Of the total oral dose administered, 25-30% is recovered as unchanged compound in the urine. Renal clearance is 250-450 ml/min, indicating some tubular excretion. A small amount may be excreted as the sulphoxide.

A 10 mg chewable tablet has been shown to be bioequivalent to a 10 mg film coated tablet.

5.3 Preclinical safety data

Extensive preclinical safety studies have been performed in dogs, rats, mice and rabbits using oral and intravenous routes of administration of famotidine. Minimal toxicological effects (after acute, subacute or chronic administration) have been observed, even at extremely high dosage levels and for extended periods of administration.

No evidence of teratogenic, mutagenic or carcinogenic effects or alteration of reproductive function have been seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylcellulose Ph Eur, Magnesium Stearate Ph Eur, Lactose Ph Eur, Cellulose Acetate NF, Aspartame NF, Mannitol Ph Eur, Hydroxypropyl Methylcellulose Ph Eur, Microcrystalline Cellulose Ph Eur, Red Iron Oxide (E172), Prosweet Powder, Trusil Natural Peppermint.

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at temperatures below 30° C
Protect from moisture

Keep out of the reach of children

6.5 Nature and contents of container

Strip packs composed of Paper/LDPE/Aluminium foil

For P use
The packs will contain : 2, 6, 8, 10, 12, 18 and 20 tablets

For GSL use the packs will contain: 2, 6, 8, 10 and 12 tablets

6.6 Instructions for use/handling

Instructions for use will appear on the packaging and in the patient package leaflet.
No special handling precautions.

7 PRODUCT LICENCE HOLDER

Merck, Sharp & Dohme Limited
Hertford Road
Hoddesdon
HERTS
EN11 9BU

Distributed by :

Johnson & Johnson . MSD
Consumer Pharmaceuticals
Enterprise House
Station Road
Loudwater
High Wycombe
BUCKS HP10 9UF

Tel : 01494 450778

8 MARKETING AUTHORISATION NUMBER

PL 00025/0313

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

2 April 1996

10 DATE OF (PARTIAL) REVISION OF THE TEXT

27.09.99

Annex 4

APPENDIX 4

PROPOSED PATIENT INFORMATION LEAFLETS FOR THE GSL PACKS

- Pepcid AC for GSL Use
- Pepcid AC Chewable for GSL Use

PRODUCT INFORMATION LEAFLET

Pepcid®AC acid control
Famotidine 10 mg

How this leaflet can help you

This leaflet tells you about Pepcid®AC tablets and your symptoms. It also gives you important advice about the effects of the tablets. Please read it all carefully, before you take the tablets. Don't throw it away, as you may need to look at it again.

If you need more help, or if there is anything you don't understand, ask a pharmacist (chemist) or your doctor.

1. About Pepcid®AC

Pepcid®AC relieves symptoms of indigestion, heartburn and excess acid with just one small easy to swallow tablet. Pepcid®AC is salt free and contains the active ingredient famotidine which belongs to a group of medicines known as H2 blockers. Other inactive ingredients in each tablet include:

- Inactive ingredients: Hydroxypropylcellulose , Magnesium Stearate , Hydroxypropyl Methylcellulose , Microcrystalline Cellulose , Pregelatinised Maize Starch, Red Iron Oxide (E172), Talc , Titanium Dioxide (E171), Carnauba Wax

Pepcid®AC tablets come in packs of 6, or 12

Product licence number: PL 0025/0312

Product licence holder: Merck Sharp & Dohme Limited, Hertford Road, Hoddesdon, Herts, EN11 9BU

Manufactured by: Frosst Iberica SA, Via Complutense 140, 28805 Alcala de Henares, Madrid, Spain

2. What Pepcid®AC does

Pepcid®AC tablets are for the short-term relief of indigestion, heartburn, and excess acid symptoms. Unlike antacids which neutralise acid Pepcid®AC controls the amount of excess acid produced to treat the cause of the pain and discomfort. Clinical trials prove that Pepcid®AC controls excess stomach acid for 9 hours throughout the day, and 12 hours throughout the night.

3. Before you take Pepcid®AC

Do not take Pepcid®AC if you are breastfeeding.

Check with your doctor or pharmacist before taking these tablets:

- If you have kidney or liver problems;
- If you are allergic to any of the ingredients in this product listed in this leaflet.

Pepcid®AC is <u>not</u> known to interact with other medicines or alcohol.

If you suffer indigestion ask the advice of your doctor or pharmacist before taking a medicine:

- If you have lost weight without trying to
- If you are 45 or over and have indigestion for the first time, or your symptoms have recently changed
- If you have difficulty swallowing or persistent stomach pains
- If you are pregnant
- If you have any other illness, are seeing a doctor regularly or taking any other medicines.

4. Taking Pepcid®AC

Adults and young people aged 16 years and over:
Swallow one tablet (10mg) to relieve the symptoms of indigestion, heartburn, or excess acid. Repeat the dose if symptoms return. Do not take more than 2 tablets (20mg) in 24 hours.

Pepcid®AC is not for children under 16 years

If your symptoms get worse or the tablets have no effect please talk to your doctor.

If you need to take a medicine for indigestion every day for more than 2 weeks it may be a sign that you have a different medical problem. Please talk to your doctor.

If you take too many tablets please tell your doctor.

5. Possible side effects

Most people do not get side effects when taking Pepcid®AC.

Rarely people have reported headache and dizziness. Other side effects reported even more rarely include: dry mouth, nausea, vomiting, abdominal bloating or discomfort, constipation, diarrhoea, loss of appetite, tiredness, jaundice (yellowing of the skin), breast increases in men. Blood tests showing lowered blood cell counts and worsening liver disease have been reported rarely, but these may not have been caused by the medicine.

As with all medicines, allergic reactions may occur but they are very rare with Pepcid®AC. Itching, rashes, facial swelling, joint pains, shortness of breath or fainting may mean you are allergic to this medicine.

If you experience a reaction of any sort, stop your treatment and see your doctor or pharmacist.

6. How to store your tablets

Keep the tablets away from children. Store them in a dry place below 30°C and protect from light. Don't use them after the expiry date printed on the box

7. Finding out more

If you have any questions about the medicine ask your pharmacist or doctor or write to us at:

Johnson & Johnson ◦ MSD
Consumer Pharmaceuticals,
Enterprise House
Station Road
Loudwater
High Wycombe
BUCKS HP10 9UF

Date of revision: September 1999

Pepcid®AC is distributed by Johnson & Johnson ◦ MSD Consumer Pharmaceuticals, on behalf of Merck Sharp & Dohme Limited.

PRODUCT INFORMATION LEAFLET

Pepcid®AC chewable acid control
Famotidine 10 mg

How this leaflet can help you

This leaflet tells you about Pepcid®AC chewable tablets and your symptoms. It also gives you important advice about the effects of the tablets. Please read it all carefully, before you take the tablets. Don't throw it away, as you may need to look at it again.

If you need more help, or if there is anything you don't understand, ask a pharmacist (chemist) or your doctor.

1. About Pepcid®AC Chewable

Pepcid®AC relieves symptoms of indigestion, heartburn and excess acid with just one small easy to swallow tablet. Pepcid®AC is salt free and contains the active ingredient famotidine which belongs to a group of medicines known as H2 blockers. Other inactive ingredients in each tablet include:

- Inactive ingredients: Hydroxypropylcellulose , Magnesium Stearate, Lactose, Cellulose Acetate, Aspartame, Mannitol, Hydroxypropyl Methylcellulose , Microcrystalline Cellulose, Red Iron Oxide (E172), Prosweet Powder, Trusil Natural Peppermint

Pepcid®AC tablets come in packs of 2 or 8

Product licence number: PL 0025/0313

Product licence holder: Merck Sharp & Dohme Limited, Hertford Road, Hoddesdon, Herts, EN11 9BU

Manufactured by: Merck Manufacturing Division, Shotton Lane, Cramlington, Northumberland NE23 9JU

2. What Pepcid®AC does

Pepcid®AC tablets are for the short-term relief of indigestion, heartburn, and excess acid symptoms. Unlike antacids which neutralise acid Pepcid®AC controls the amount of excess acid produced to treat the cause of the pain and discomfort. Clinical trials prove that Pepcid®AC controls excess stomach acid for 9 hours throughout the day, and 12 hours throughout the night.

3. Before you take Pepcid®AC chewable tablets

Do not take Pepcid®AC if you are breastfeeding.

Check with your doctor or pharmacist before taking these tablets:

- If you have kidney or liver problems;
- If you are allergic to any of the ingredients in this product listed in this leaflet.

Pepcid®AC is <u>not</u> known to interact with other medicines or alcohol.

If you suffer indigestion ask the advice of your doctor or pharmacist before taking a medicine:

- If you have lost weight without trying to
- If you are 45 or over and have indigestion for the first time, or your symptoms have recently changed
- If you have difficulty swallowing or persistent stomach pains
- If you are pregnant
- If you have any other illness, are seeing a doctor regularly or taking any other medicines.

4. Taking Pepcid®AC chewable tablets

Adults and young people aged 16 years and over:
Chew one tablet (10mg) to relieve the symptoms of indigestion, heartburn, or excess acid. Repeat the dose if symptoms return. Do not take more than 2 tablets (20mg) in 24 hours.

Pepcid®AC is not for children under 16 years

If your symptoms get worse or the tablets have no effect please talk to your doctor.

If you need to take a medicine for indigestion every day for more than 2 weeks it may be a sign that you have a different medical problem. Please talk to your doctor.

If you take too many tablets please tell your doctor.

5. Possible side effects

Most people do not get side effects when taking Pepcid®AC chewable tablets

Rarely people have reported headache and dizziness. Other side effects reported even more rarely include: dry mouth, nausea, vomiting, abdominal bloating or discomfort, constipation, diarrhoea, loss of appetite, tiredness, jaundice (yellowing of the skin), breast increases in men. Blood tests showing lowered blood cell counts and worsening liver disease have been reported rarely, but these may not have been caused by the medicine.

As with all medicines, allergic reactions may occur but they are very rare with Pepcid®AC. Itching, rashes, facial swelling, joint pains, shortness of breath or fainting may mean you are allergic to this medicine.

If you experience a reaction of any sort, stop your treatment and see your doctor or pharmacist.

6. How to store your tablets

Keep the tablets away from children. Store them in a dry place below 30°C and protect from light. Don't use them after the expiry date printed on the box

7. Finding out more

If you have any questions about the medicine ask your pharmacist or doctor or write to us at:

Johnson & Johnson ◦ MSD
Consumer Pharmaceuticals,
Enterprise House
Station Road
Loudwater
High Wycombe
BUCKS HP10 9UF

Date of revision: September 1999

Pepcid®AC is distributed by Johnson & Johnson ◦ MSD Consumer Pharmaceuticals, on behalf of Merck Sharp & Dohme Limited.

APPENDIX 6

PROPOSED LABELLING TEXT FOR THE GSL PACK

- Pepcid AC
- Pepcid AC Chewable

PEPCID AC TABLETS
CARTON LABELLING

FRONT PANEL

Effective Long Lasting Relief from Indigestion and Heartburn

Pepcid® AC - acid control
famotidine

One tablet controls excess stomach acid for 9 hours

Easy to swallow
6, 12 tablets

BACK PANEL

Pepcid® AC - acid control

Famotidine USP 10 mg tablets

Pepcid AC offers effective, long lasting relief from the symptoms of indigestion, heartburn, and excess acid.

One easy to swallow Pepcid AC tablet gets to work fast. It controls excess stomach acid for 9 hours throughout the day and for 12 hours throughout the night
DOSAGE: Adults & children 16 years and older: Swallow one Pepcid AC tablet to relieve the symptoms of indigestion, heartburn or excess acid.
Repeat the dose if symptoms return. Do not take more than 2 tablets in 24 hours.
If symptoms persist for more than 2 weeks, please consult your doctor.

Pepcid AC is salt free

Keep the tablets in a dry place below 30°C and protect from light.
Keep all medicines safely away from children.

PLEASE READ THE ENCLOSED LEAFLET CAREFULLY BEFORE TAKING THE TABLETS

PL 0025/0312

Product licence holder: Merck Sharp & Dohme Limited, Hertford Road, Hoddesdon, HERTS EN11 9BU

Distributed by: Johnson & Johnson • MSD Consumer Pharmaceuticals, Enterprise House, Loudwater, BUCKS HP10 9UF

BASE PANEL

Pepcid® AC - acid control
Barcode

SIDE PANEL 1

Pepcid® AC - acid control

Expiry date:
Batch number:

SIDE PANEL 2

Pepcid® AC - acid control

TOP PANEL

Pepcid® AC - acid control
6, 12 tablets

BLISTER COPY

Pepcid® AC

Famotidine 10 mg
Merck Sharp & Dohme Ltd

BN
EXP

PEPCID AC CHEWABLE TABLETS
CARTON LABELLING

FRONT PANEL

Effective Long Lasting Relief from Indigestion and Heartburn

Pepcid® AC chewable acid control
famotidine

One minty tablet controls excess stomach acid for 9 hours

Easy to swallow
2, 8 tablets

BACK PANEL

Pepcid® AC chewable acid control

Famotidine USP 10 mg chewable tablets

Pepcid AC offers effective, long lasting relief from the symptoms of indigestion, heartburn, and excess acid.

One easy to chew Pepcid AC tablet gets to work fast. It controls excess stomach acid for 9 hours throughout the day and for 12 hours throughout the night

DOSAGE: Adults & children 16 years and older: Chew one Pepcid AC tablet to relieve the symptoms of indigestion, heartburn or excess acid.
Repeat the dose if symptoms return. Do not take more than 2 tablets in 24 hours.
If symptoms persist for more than 2 weeks, please consult your doctor.

Keep the tablets in a dry place below 30°C and protect from light.
Keep all medicines safely away from children.

PLEASE READ THE ENCLOSED LEAFLET CAREFULLY BEFORE TAKING THE TABLETS

PL 0025/0313

Product licence holder: Merck Sharp & Dohme Limited, Hertford Road, Hoddesdon, HERTS EN11 9BU

Distributed by: Johnson & Johnson • MSD Consumer Pharmaceuticals, Enterprise House, Loudwater, BUCKS HP10 9UF

BASE PANEL

Pepcid® AC chewable acid control
Barcode

SIDE PANEL 1

Pepcid® AC chewable acid control

Expiry date:
Batch number:

SIDE PANEL 2

Pepcid® AC chewable acid control

TOP PANEL

Pepcid® AC chewable acid control
2, 8 tablets

Annex 5

EXTRACT PERIOD: 01/07/63-14/10/98 EARLIEST REACTION DATE: 26/07/87 REACTION: ALL TYPE:SPONTANEOUS ORIGIN: UK

DRUG : FAMOTIDINE ROUTE: ALL SUBSTANCE/VARIANT/NPCG: SUBS

SINGLE-CONSTITUENT PRODS : PEPCID

MULTI-CONSTITUENT PRODS : NONE

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Cardiovascular disorders				
Cardiovascular disease symptoms & signs				
Lower limb oedema	1	0	0	0
Oedema NOS	8	0	0	0
Palpitations	4	0	0	0
Pulmonary vascular disorders				
Pulmonary embolism	1	1	0	0
Hypertensive disease				
Hypertension	1	0	0	0
Hypotension (all forms)				
Hypotension	1	0	0	0
Postural hypotension	1	0	0	0
Syncope	1	0	0	0
Cardiac arrhythmias (general)				
Arrhythmia	1	0	0	0
Bradycardia NOS (exc foetal)	1	0	0	0
Extrasystoles NOS	1	0	0	0
Tachycardia NOS	2	0	0	0
SYS ORGAN CLASS TOTAL:	23	1	0	0
Cerebrovascular disorders				
Brain ischaemia (aetiology unspecified)				
Cerebrovascular accident	1	0	0	0
SYS ORGAN CLASS TOTAL:	1	0	0	0
Disorders of metabolism & nutrition				
Appetite & nutritional disorders				
Weight increased	2	0	0	0
Weight loss	1	0	0	0
Acidotic disorders				
Lactic acidosis	1	0	0	0
Diabetes mellitus (all forms)				
Diabetes mellitus aggravated	1	0	0	0
Hyperlipidaemias				
Hyperlipidaemia NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	6	0	0	0
Disorders of the ear				
Hearing abnormal				
Deafness	1	0	0	0
Vestibular disorders				
Vertigo	4	0	0	0
SYS ORGAN CLASS TOTAL:	5	0	0	0
Disorders of the eye				
Abnormal vision (all forms)				
Abnormal vision NOS	5	0	0	0
Vision blurred	1	0	0	0
Conjunctival and scleral disorders				
Conjunctivitis NOS	2	0	0	0
Dry eyes	1	0	0	0
Eye symptoms & signs				
Eye irritation	1	0	0	0
Eye pain	1	0	0	0
Lacrimal gland disorders				
Xerophthalmia	1	0	0	0
SYS ORGAN CLASS TOTAL:	12	0	0	0
Gastrointestinal disorders				
Anal & rectal disorder NOS				
Rectal haemorrhage	2	0	0	0
Enteritis, colitis & proctitis (exc infections)				
Colitis	2	0	0	0
Gastrointestinal disorders NOS				
Abdominal adhesions	1	0	0	0
Gastrointestinal system symptoms & signs				
Abdominal pain NOS	17	0	0	0
Constipation	7	0	0	0
Diarrhoea NOS	29	0	0	0
Dyspepsia	4	0	0	0
Eructation	1	0	0	0
Flatulence	4	0	0	0
Nausea	25	0	0	0
Vomiting	11	0	0	0
Ill-defined gastrointestinal infections				
Gastroenteritis NOS	1	0	0	0
Oral soft tissue disorders				
Stomatitis ulcerative	2	0	0	0
Salivary gland disorders				
Dry mouth	9	0	0	0
Parotitis	1	0	0	0
SYS ORGAN CLASS TOTAL:	116	0	0	0
General disorders				

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
General symptoms & signs				
Bloating NOS	1	0	0	0
Chest pain	2	0	0	0
Discomfort in mouth	1	0	0	0
Dizziness (exc vertigo)	41	0	0	0
Fatigue	5	0	0	0
Feeling abnormal	1	0	0	0
Flushing	2	0	0	0
Hyperkinetic syndrome	1	0	0	0
Insomnia	12	0	0	0
Irritability	1	0	0	0
Malaise	11	0	0	0
Nightmares	6	0	0	0
Pain NOS	2	0	0	0
Pain in limb	1	0	0	0
Pyrexia	2	0	0	0
Rigors	1	0	0	0
Sedation	9	0	0	0
Thirst	6	0	0	0
Therapeutic & non-therapeutic drug responses				
Drug ineffective	19	0	0	0
Drug interaction NOS	2	0	0	0
Drug interaction potentiation	2	0	0	0
Unexpected therapeutic effect	1	0	0	0
SYS ORGAN CLASS TOTAL:	129	0	0	0
Haemopoietic disorders				
Platelet related disorders				
Thrombocythaemia	1	0	0	0
Thrombocytopenia	2	0	0	0
Thrombotic thrombocytopenic purpura	1	0	0	0
Disorders with decreased white blood cells				
Leucopenia NOS	1	0	0	0
Neutropenia	1	0	0	0
Disorders with increased white blood cells				
Monocytosis	1	0	0	0
SYS ORGAN CLASS TOTAL:	7	0	0	0
Hepato-biliary disorders				
Hepatic function abnormalities				
Alkaline phosphatase increased	1	0	0	0
Hepatic function abnormal NOS	2	0	0	0
Hepatitis (all forms)				
Autoimmune hepatitis NOS	1	0	0	0
Hepatitis NOS	1	0	0	0
Jaundice (all forms)				
Jaundice NOS	2	0	0	0
SYS ORGAN CLASS TOTAL:	7	0	0	0
Injury & poisoning				
Trauma NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	1	0	0	0
Musculoskeletal, connective tissue & bone disorders				
Muscle disorders				
Muscle cramps	1	0	0	0
Myalgia	3	0	0	0
Myopathy	1	0	0	0
Musculoskeletal disorders NOS				
Back pain	2	0	0	0
Arthropathies nonspecific				
Arthralgia	6	0	0	0
Arthritis	2	0	0	0
Arthropathy	1	0	0	0
Crystal arthropathies				
Gout	1	0	0	0
SYS ORGAN CLASS TOTAL:	17	0	0	0
Neoplasms				
Breast neoplasms				
Malignant breast neoplasm	1	0	0	0
SYS ORGAN CLASS TOTAL:	1	0	0	0
Neurological disorders				
Altered consciousness				
Loss of consciousness NOS	1	0	0	0
Convulsions & epilepsy				
Convulsions NOS	1	0	0	0
Disorders of coordination				
Ataxia NOS	1	0	0	0
Gait abnormal	1	0	0	0
Tremor NOS	2	0	0	0
Headache (all forms)				
Headache NOS	37	0	0	0
Migraine	5	0	0	0
Peripheral neuropathies				
Guillain Barre syndrome	1	0	0	0
Sensory abnormalities				
Paraesthesia	8	0	0	0
Taste altered	2	0	0	0
Taste loss	1	0	0	0
SYS ORGAN CLASS TOTAL:	60	0	0	0
Peripheral vascular disorders				
Arterial inflammatory diseases				
Vasculitis NOS	1	0	0	0
Venous disorders				
Venous thrombophlebitis	1	0	0	0

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
SYS ORGAN CLASS TOTAL:	2	0	0	0
Psychiatric disorders				
Affective disorders (all forms)				
Depression NOS	2	0	0	0
Endogenous depression	1	0	0	0
Miscellaneous psychiatric disorders				
Emotional instability	1	0	0	0
Psychiatric symptoms & signs				
Abnormal thinking	1	0	0	0
Aggression	1	0	0	0
Agitation	4	0	0	0
Anxiety	2	0	0	0
Confusion	5	0	0	0
Depersonalisation	2	0	0	0
Hallucinations	1	0	0	0
Nervousness	3	0	0	0
Psychoses (excluding affective psychoses)				
Paranoia	2	0	0	0
Psychosis NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	26	0	0	0
Renal & urinary disorders				
Urinary disease symptoms & signs				
Nocturia	1	0	0	0
Polyuria	1	0	0	0
Renal pain	1	0	0	0
Urinary frequency	5	0	0	0
Urinary retention	2	0	0	0
SYS ORGAN CLASS TOTAL:	10	0	0	0
Reproductive disorders				
Reproductive disorders NOS				
Libido decreased	1	0	0	0
Libido increased	1	0	0	0
Miscellaneous breast disorders				
Breast engorgement	1	0	0	0
Breast enlargement	3	0	0	0
Breast pain	5	0	0	0
Galactorrhoea	1	0	0	0
Gynaecomastia	9	0	0	0
Mastitis	1	0	0	0
Nipple disorder	2	0	0	0
Disorders of menstruation				
Menorrhagia	1	0	0	0
Male sexual disorders				
Erectile dysfunction	3	0	0	0
Prostatic disorders				
Prostatic disorder NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	29	0	0	0
Respiratory disorders				
Respiratory symptoms & signs				
Chest tightness	1	0	0	0
Dyspnoea	1	0	0	0
Obstructive airways disorders				
Bronchospasm	1	0	0	0
Nasal cavity & sinus disorders (exc infections)				
Epistaxis	1	0	0	0
Rhinitis NOS	1	0	0	0
Upper respiratory tract infections (all forms)				
Pharyngitis NOS	2	0	0	0
SYS ORGAN CLASS TOTAL:	7	0	0	0
Skin & subcutaneous tissue disorders				
Bullous dermatoses				
Blister	1	0	0	0
Erythema multiforme	2	0	0	0
Dermatitis & eczema				
Dermatitis lichenoid	1	0	0	0
Eczema NOS	2	0	0	0
Localised exfoliation	1	0	0	0
Miscellaneous skin & subcutaneous tissue disorders				
Erythema nodosum	1	0	0	0
Pruritus	22	0	0	0
Skin inflammation NOS	1	0	0	0
Nail disorders				
Nail abnormality NOS	3	0	0	0
Photosensitivity eruptions				
Photosensitivity reaction	2	0	0	0
Rashes				
Localised skin reaction	1	0	0	0
Rash NOS	33	0	0	0
Rash erythematous	7	0	0	0
Rash maculo-papular	2	0	0	0
Sweating disorders				
Night sweats	1	0	0	0
Sweating increased	5	0	0	0
Vascular abnormalities of skin				
Purpura	2	0	0	0
Spider naevus	1	0	0	0
Angioedema				
Angioedema	2	0	0	0
Face oedema	7	0	0	0
Periorbital oedema	1	0	0	0
Urticaria				
Urticaria	17	0	0	0
Hair & hair follicle disorders				
Alopecia	2	0	0	0
Hair texture abnormal	1	0	0	0
Psoriasis & similar conditions				

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Psoriasis	1	0	0	0
SYS ORGAN CLASS TOTAL:	119	0	0	0
TOTAL REACTIONS FOR DRUG:	578	1	0	0

TOTAL REPORTS: 372 TOTAL FATAL OUTCOME: 1

Annex 6

EXTRACT PERIOD: 01/07/63-18/01/00 EARLIEST REACTION DATE: 22/09/80 REACTION: ALL TYPE:SPONTANEOUS ORIGIN: UK

DRUG : RANITIDINE ROUTE: ALL SUBSTANCE/VARIANT/NPCG: SUBS

SINGLE-CONSTITUENT PRODS : APS RANITIDINE, ASHBOURNE RANITIDINE, BOOTS RANITIDINE, COX RANITIDINE, CP RANITIDINE, GENERICS (UK) RANITIDINE, GLAXO PHARMACEUTICALS ZANTAC, HILLCROSS RANITIDINE, NORTON HEALTHCARE RANITIDINE, RANBAXY UK RANITIDINE, RANIPLEX, ZAEDOC 300, ZANTAC, ZANTAC (AZANTAC), ZANTAC / AZANTAC TABLETS

MULTI-CONSTITUENT PRODS : NONE

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Cardiovascular disorders				
Cardiac failure (all forms)				
Acute circulatory failure	1	0	0	0
Cardiac failure NOS	3	1	0	0
Left ventricular failure	2	0	0	0
Pulmonary oedema	1	0	0	0
Right ventricular failure	1	0	0	0
Cardiovascular disease symptoms & signs				
Lower limb oedema	10	0	0	0
Oedema NOS	41	0	0	0
Palpitations	17	0	0	0
Coronary artery disease (all forms)				
Angina pectoris	1	0	0	0
Angina pectoris aggravated	3	0	0	0
Myocardial infarction	4	0	0	0
Heart block (all forms)				
Heart block NOS	4	0	0	0
Heart block complete	1	0	0	0
Stokes Adams syndrome	1	0	0	0
Hypertensive disease				
Hypertension	3	0	0	0
Hypertension aggravated	1	0	0	0
Hypotension (all forms)				
Hypotension	11	0	0	0
Postural hypotension	3	0	0	0
Syncope	13	0	0	0
Cardiac arrhythmias (general)				
Arrhythmia	2	0	0	0
Bradycardia NOS (exc foetal)	2	0	0	0
Cardiac arrest	7	2	0	0
Tachycardia NOS	10	0	0	0
Supraventricular arrhythmias (all forms)				
Atrial fibrillation	4	0	0	0
Nodal arrhythmia	1	0	0	0
Sinus bradycardia	28	0	0	0
Supraventricular tachycardia	3	0	0	0
Ventricular arrhythmias				
Ventricular arrhythmia NOS	1	0	0	0
Ventricular ectopics	2	0	0	0
Ventricular tachycardia	1	0	0	0
SYS ORGAN CLASS TOTAL:	182	3	0	0
Cerebrovascular disorders				
Cerebral haemorrhagic lesions				
Subarachnoid haemorrhage	1	1	0	0
Brain ischaemia (aetiology unspecified)				
Cerebrovascular accident	3	1	0	0
Transient ischaemic attack	1	0	0	0
SYS ORGAN CLASS TOTAL:	5	2	0	0
Congenital anomalies				
Chromosomal disorders				
Chromosomal abnormalities NOS	1	0	0	0
Congenital alimentary tract anomalies				
Cleft palate	1	0	0	0
Congenital pyloric stenosis	1	0	0	0
Exomphalos	1	0	0	0
Congenital face & neck disorders				
Facial dysmorphism	1	0	0	0
Congenital respiratory tract disorders				
Pulmonary hypoplasia	1	0	0	0
Miscellaneous congenital anomalies				
Congenital abnormality NOS	1	0	0	0
Multiple congenital abnormalities	1	0	0	0
Congenital limb deformities				
Congenital limb malformation NOS	1	0	0	0
Phocomelia	1	0	0	0
SYS ORGAN CLASS TOTAL:	10	0	0	0
Disorders of metabolism & nutrition				
Appetite & nutritional disorders				
Anorexia	7	0	0	0
Weight increased	8	0	0	0
Weight loss	2	0	0	0
Hepatic metabolic disorders				
Porphyria NOS	3	0	0	0
Intolerance syndromes				
Alcohol intolerance	2	0	0	0
Diabetes mellitus (all forms)				
Diabetes mellitus NOS	2	0	0	0
Diabetes mellitus aggravated	3	0	0	0

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Disorders related to diabetes				
Diabetic control impaired	1	0	0	0
Glycosuria	1	0	0	0
Hypoglycaemia	2	0	0	0
Hyperlipidaemias				
Hypercholesterolaemia	1	0	0	0
Electrolyte & fluid balance disorders				
Hypercalcaemia	1	0	0	0
Hypokalaemia	3	0	0	0
Hyponatraemia	4	0	0	0
SYS ORGAN CLASS TOTAL:	40	0	0	0
Disorders of the ear				
Hearing abnormal				
Deafness	3	0	0	0
Hearing impaired	1	0	0	0
Miscellaneous ear disorders				
Earache	1	0	0	0
Tinnitus	6	0	0	0
Vestibular disorders				
Vertigo	19	0	0	0
SYS ORGAN CLASS TOTAL:	30	0	0	0
Disorders of the eye				
Abnormal vision (all forms)				
Abnormal vision NOS	31	0	0	0
Accommodation abnormal	9	0	0	0
Blindness	1	0	0	0
Myopia	1	0	0	0
Transient blindness	2	0	0	0
Vision blurred	5	0	0	0
Visual acuity reduced	1	0	0	0
Visual disturbance NOS	5	0	0	0
Anterior and posterior chamber disorders				
Glaucoma NOS	1	0	0	0
Raised intraocular pressure aggravated	1	0	0	0
Conjunctival and scleral disorders				
Conjunctivitis NOS	16	0	0	0
Dry eyes	4	0	0	0
Corneal disorders				
Corneal disorders NOS	1	0	0	0
Keratitis	1	0	0	0
Keratoconjunctivitis	3	0	0	0
Eye symptoms & signs				
Eye abnormality NOS	2	0	0	0
Eye haemorrhage NOS	3	0	0	0
Eye inflammation	14	0	0	0
Eye irritation	8	0	0	0
Eye pain	11	0	0	0
Nystagmus	2	0	0	0
Red eye	3	0	0	0
Eyelid disorders				
Blepharitis	1	0	0	0
Blepharospasm	2	0	0	0
Eyelid oedema	7	0	0	0
Eyelid swelling	15	0	0	0
Iris, ciliary body & choroid disorders				
Iritis	1	0	0	0
Uveitis	3	0	0	0
Lacrimal gland disorders				
Lacrimation increased	2	0	0	0
Xerophthalmia	4	0	0	0
Retinal & ophthalmic vascular disorders				
Retinal artery thrombosis	1	0	0	0
Retinal haemorrhage	1	0	0	0
Retinal disorders NOS				
Retinal detachment	2	0	0	0
Retinopathy NOS	3	0	0	0
Optic nerve & visual pathways disorders				
Optic neuritis	1	0	0	0
Optic neuropathy NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	169	0	0	0
Disorders of the immune system				
Allergies (exc angioedema)				
Allergic reaction NOS	21	0	0	0
Anaphylactic reaction	17	0	0	0
Anaphylactic shock	1	0	0	0
Anaphylactoid reaction	13	0	0	0
Lymphadenopathy & related conditions				
Lymphadenopathy	1	0	0	0
SYS ORGAN CLASS TOTAL:	53	0	0	0
Endocrine disorders				
Endocrine reproductive disorders				
Hirsutism	8	0	0	0
Parathyroid gland disorders				
Hyperparathyroidism	1	0	0	0
Pituitary gland disorders				
Antidiuretic hormone increased	1	0	0	0
Hyperprolactinaemia	3	0	0	0
Inappropriate ADH secretion	1	0	0	0
Pituitary disorder NOS	1	0	0	0
Thyroid gland disorders				
Hypothyroidism	1	0	0	0
SYS ORGAN CLASS TOTAL:	16	0	0	0
Gastrointestinal disorders				
Anal & rectal disorder NOS				
Proctalgia	1	0	0	0
Rectal disorder	1	0	0	0

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Rectal haemorrhage	3	0	0	0
Tenesmus	2	0	0	0
Enteritis, colitis & proctitis (exc infections)				
Colitis	1	0	0	0
Ileitis	1	0	0	0
Inflammatory bowel disease NOS	1	0	0	0
Proctitis	1	0	0	0
Pseudomembranous colitis	1	0	0	0
Gastrointestinal disorders NOS				
Retroperitoneal fibrosis	2	0	0	0
Gastrointestinal function disorders				
Faecal incontinence	2	0	0	0
Gastrointestinal haemorrhage NOS				
Gastrointestinal haemorrhage	3	0	0	0
Gastrointestinal stenosis & obstruction				
Gastrointestinal obstruction NOS	1	0	0	0
Gastrointestinal system symptoms & signs				
Abdomen enlarged	5	0	0	0
Abdominal colic	1	0	0	0
Abdominal pain NOS	58	0	0	0
Bowel sounds abnormal	1	0	0	0
Constipation	23	0	0	0
Diarrhoea NOS	154	0	0	0
Dyspepsia	11	0	0	0
Dyspepsia aggravated	1	0	0	0
Dysphagia	5	0	0	0
Eructation	5	0	0	0
Faecal abnormality NOS	1	0	0	0
Faeces discoloured	1	0	0	0
Flatulence	20	0	0	0
Frequent motion	1	0	0	0
Haematemesis	2	0	0	0
Heartburn	1	0	0	0
Lower abdominal pain	1	0	0	0
Masking of symptoms of gastric cancer	1	0	0	0
Melaena	5	0	0	0
Nausea	91	0	0	0
Nausea and vomiting	2	0	0	0
Pruritus ani	1	0	0	0
Upper abdominal pain	5	0	0	0
Upper abdominal pain worsened	1	0	0	0
Vomiting	31	0	0	0
Gastrointestinal vascular disorders				
Haemorrhoidal haemorrhage	1	0	0	0
Malabsorption syndromes				
Malabsorption	1	0	0	0
Pancreatic disorders				
Pancreatic pseudocyst	1	0	0	0
Pancreatitis NOS	2	0	0	0
Pancreatitis acute	3	0	0	0
Pancreatitis chronic	1	0	0	0
Pancreatitis haemorrhagic	1	1	0	0
Tongue disorders				
Glossitis	6	0	0	0
Tongue discolouration	1	0	0	0
Tongue disorder NOS	1	0	0	0
Tongue pain	1	0	0	0
Tongue ulceration	1	0	0	0
Dental infections				
Tooth caries	1	0	0	0
Upper gastrointestinal ulceration & perforation				
Duodenal erosions	1	0	0	0
Duodenal ulcer	1	0	0	0
Gastric erosions	1	0	0	0
Gastric ulcer haemorrhage	2	0	0	0
Gastric ulcer perforated	1	0	0	0
Oesophagitis	4	0	0	0
Oesophagitis aggravated	1	0	0	0
Peptic ulcer reactivated	1	0	0	0
Oral soft tissue disorders				
Cheilitis	1	0	0	0
Gingival hyperplasia	1	0	0	0
Gingivitis	3	0	0	0
Stomatitis	10	0	0	0
Stomatitis ulcerative	20	0	0	0
Salivary gland disorders				
Dry mouth	17	0	0	0
Parotitis	1	0	0	0
Saliva altered	1	0	0	0
Salivary hypersecretion	1	0	0	0
Tooth disorders				
Dental enamel loss	2	0	0	0
Tooth discolouration	2	0	0	0
Tooth disorder NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	541	1	0	0
General disorders				
General symptoms & signs				
Bloating NOS	2	0	0	0
Chest pain	44	0	0	0
Choking sensation	2	0	0	0
Collapse	2	0	0	0
Concentration impairment	12	0	0	0
Crying	1	0	0	0
Discomfort in mouth	4	0	0	0
Dizziness (exc vertigo)	158	0	0	0
Exacerbation of pain	3	0	0	0
Fatigue	51	0	0	0
Feeling abnormal	5	0	0	0
Feeling cold	2	0	0	0
Flushing	24	0	0	0
Halitosis	1	0	0	0
Hoarseness	1	0	0	0
Hyperkinetic syndrome	2	0	0	0
Hyperpyrexia	1	0	0	0

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Hypothermia	1	0	0	0
Influenza like illness	2	0	0	0
Insomnia	22	0	0	0
Irritability	12	0	0	0
Malaise	46	0	0	0
Nightmares	28	0	0	0
Pain NOS	14	0	0	0
Pain in limb	14	0	0	0
Prostration	1	0	0	0
Pyrexia	13	0	0	0
Rigors	1	0	0	0
Screaming	1	0	0	0
Sedation	40	0	0	0
Sensation of heaviness	2	0	0	0
Shivering	4	0	0	0
Sleep walking	1	0	0	0
Stupor	2	0	0	0
Thirst	2	0	0	0
Throat swelling	1	0	0	0
Throat tightness	4	0	0	0
Upper limb oedema	3	0	0	0
Weakness	5	0	0	0
Yawning	1	0	0	0
Therapeutic & non-therapeutic drug responses				
Alcohol interaction	1	0	0	0
Drug ineffective	14	0	0	0
Drug interaction NOS	46	0	0	0
Drug interaction inhibition	5	0	0	0
Drug interaction potentiation	7	0	0	0
Drug level decreased	1	0	0	0
Drug withdrawal reaction	5	0	0	0
Unexpected therapeutic effect	5	0	0	0
SYS ORGAN CLASS TOTAL:	619	0	0	0
Haemopoietic disorders				
Haemorrhage NOS	1	0	0	0
Macrocytosis	1	0	0	0
Clotting & coagulation defects (exc platelets)				
Activated partial thromboplastin time increas	1	0	0	0
Disseminated intravascular coagulation	2	2	0	0
International normalised ratio decreased	1	0	0	0
International normalised ratio increased	2	0	0	0
Prothrombin decreased	3	0	0	0
Prothrombin time decreased	2	0	0	0
Erythrocytosis & polycythaemias				
Polycythaemia NOS	1	0	0	0
Polycythaemia rubra vera	1	0	0	0
Platelet related disorders				
Decreased platelet count	3	0	0	0
Idiopathic thrombocytopenic purpura	1	0	0	0
Platelet abnormalities	2	0	0	0
Thrombocytopenia	93	0	0	0
Thrombocytopenic purpura NOS	2	0	0	0
Stem cell disorders (exc myeloproliferative disorders)				
Aplastic anaemia	6	1	0	0
Bone marrow depression	6	1	0	0
Pancytopenia	14	1	0	0
Haemolytic disorders (exc congenital)				
Autoimmune haemolytic disease NOS	1	0	0	0
Coombs positive haemolytic anaemia	1	0	0	0
Haemolytic anaemia	3	0	0	0
Miscellaneous anaemias				
Anaemia	2	0	0	0
Haemoglobin decreased	2	0	0	0
Lymphoproliferative disorders				
Lymphoma-like disorder	1	0	0	0
Disorders with decreased white blood cells				
Agranulocytosis	11	1	0	0
Leucopenia NOS	17	1	0	0
Neutropenia	28	2	0	0
Disorders with increased white blood cells				
Eosinophilia (exc pulmonary)	2	0	0	0
Leucocytosis NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	211	9	0	0
Hepato-biliary disorders				
Hepatic and biliary system symptoms and signs				
Hepatomegaly	2	0	0	0
Gall bladder disorders				
Cholelithiasis	1	0	0	0
Hepatic function abnormalities				
Alkaline phosphatase increased	3	0	0	0
Cholestasis	2	0	0	0
Glutamic-pyruvate transaminase increased	1	0	0	0
Hepatic function abnormal NOS	49	0	0	0
Hyperbilirubinaemia	1	0	0	0
Lactic dehydrogenase increased	1	0	0	0
Hepatitis (all forms)				
Hepatitis NOS	28	0	0	0
Hepatitis cholestatic	4	0	0	0
Hepatocellular damage				
Hepatic cirrhosis	1	0	0	0
Hepatic failure	1	1	0	0
Hepatic necrosis	2	1	0	0
Hepatocellular damage NOS	4	0	0	0
Liver fatty	2	0	0	0
Jaundice (all forms)				
Jaundice NOS	39	1	0	0
Jaundice cholestatic	6	1	0	0
Jaundice hepatocellular	1	0	0	0
SYS ORGAN CLASS TOTAL:	148	4	0	0

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Infections & infestations				
Infections (organism unspecified)				
Chorioamnionitis	1	0	0	0
Bacterial infections (organism unspecified)				
Abscess NOS	1	0	0	0
Septicaemia NOS	2	0	0	0
SYS ORGAN CLASS TOTAL:	4	0	0	0
Injury & poisoning				
Overdose & poisoning				
Overdose NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	1	0	0	0
Musculoskeletal, connective tissue & bone disorders				
Connective tissue disorders				
Systemic lupus erythematosus	1	0	0	0
Disorders of synovium and bursa				
Synovitis	1	0	0	0
Metabolic bone diseases				
Osteoporosis	1	0	0	0
Miscellaneous joint disorders				
Joint stiffness	2	0	0	0
Joint swelling	5	0	0	0
Muscle disorders				
Creatine phosphokinase increased	1	0	0	0
Limb weakness	2	0	0	0
Muscle cramps	9	0	0	0
Muscle spasms	1	0	0	0
Muscle stiffness	2	0	0	0
Muscle twitching	3	0	0	0
Muscle weakness	8	0	0	0
Myalgia	55	0	0	0
Myopathy	1	0	0	0
Myositis	4	0	0	0
Musculoskeletal disorders NOS				
Back pain	13	0	0	0
Musculoskeletal pain	1	0	0	0
Neck pain	3	0	0	0
Tendon & cartilage disorders				
Dupuytren's contracture	1	0	0	0
Arthropathies nonspecific				
Acute arthritis	1	0	0	0
Arthralgia	72	0	0	0
Arthritis	7	0	0	0
Arthritis aggravated	1	0	0	0
Arthropathy	8	0	0	0
Arthrosis	6	0	0	0
Haemarthrosis	1	0	0	0
Polyarthralgia	1	0	0	0
Crystal arthropathies				
Gout	10	0	0	0
Inflammatory polyarthropathies				
Rheumatoid arthritis	1	0	0	0
SYS ORGAN CLASS TOTAL:	222	0	0	0
Neoplasms				
Hepato-biliary neoplasms				
Malignant hepatic neoplasm	1	0	0	0
Miscellaneous or site unspecified neoplasms				
Carcinoma NOS	1	0	0	0
Malignant neoplasm NOS	6	0	0	0
Renal tract neoplasms				
Bladder cancer	2	0	0	0
Malignant gastrointestinal neoplasms				
Gastric cancer	4	2	0	0
Oesophageal cancer	1	0	0	0
Rectal cancer	1	0	0	0
Leukaemias				
Lymphoblastic leukaemia NOS	1	0	0	0
Benign skin neoplasms				
Granuloma	1	0	0	0
Malignant & pre-malignant skin neoplasms				
Malignant melanoma	1	0	0	0
SYS ORGAN CLASS TOTAL:	19	2	0	0
Neurological disorders				
Abnormal reflexes				
Fixed dilated pupil	1	0	0	0
Pupillary reflex impaired	1	0	0	0
Altered consciousness				
Encephalopathy NOS	2	0	0	0
Loss of consciousness NOS	2	0	0	0
CNS infections & inflammatory disorders				
Post-viral fatigue syndrome aggravated	1	0	0	0
Convulsions & epilepsy				
Convulsions NOS	8	0	0	0
Epilepsy aggravated	3	0	0	0
Focal convulsion	1	0	0	0
Grand mal convulsion	4	0	0	0
Myoclonic seizure	1	0	0	0
Cranial nerve disorders				
Cranial nerve lesion NOS	1	0	0	0
Disorders of coordination				
Ataxia NOS	10	0	0	0
Balance impaired NOS	3	0	0	0
Coordination abnormal NOS	5	0	0	0
Difficulty in walking	2	0	0	0
Gait abnormal	1	0	0	0
Tremor NOS	17	0	0	0
Headache (all forms)				
Headache NOS	241	0	0	0
Migraine	22	0	0	0

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Migraine aggravated	4	0	0	0
Increased intracranial pressure & hydrocephalus				
Benign intracranial hypertension	1	0	0	0
Cerebral oedema	1	1	0	0
Miscellaneous brain disorders				
Neurological disorder NOS	1	0	0	0
Neurological visual disorders				
Diplopia	11	0	0	0
Photophobia	4	0	0	0
Tunnel vision	1	0	0	0
Paralysis (all forms)				
Hemiplegia	1	0	0	0
Peripheral neuropathies				
Carpal tunnel syndrome	1	0	0	0
Peripheral neuropathy NOS	10	0	0	0
Peripheral sensory neuropathy	2	0	0	0
Polyneuropathy NOS	3	0	0	0
Sensory abnormalities				
Anosmia	1	0	0	0
Burning sensation	4	0	0	0
Hypoaesthesia	11	0	0	0
Neuralgia NOS	1	0	0	0
Paraesthesia	53	0	0	0
Parosmia	1	0	0	0
Sensory disturbance NOS	4	0	0	0
Taste altered	7	0	0	0
Taste loss	3	0	0	0
Speech and communication disorders				
Aphasia	2	0	0	0
Dysarthria	1	0	0	0
Dysphasia	1	0	0	0
Dysphonia	2	0	0	0
Speech disorder NOS	4	0	0	0
Abnormalities of muscle tone				
Hypertonia	1	0	0	0
Extrapyramidal disorders (all forms)				
Akinesia	1	0	0	0
Chorea	1	0	0	0
Choreoathetosis	2	0	0	0
Dyskinesia	2	0	0	0
Extrapyramidal disorder NOS	2	0	0	0
Oculogyric crisis	1	0	0	0
Parkinson's disease aggravated	2	0	0	0
Parkinsonism	1	0	0	0
Amnesic syndromes				
Amnesia	10	0	0	0
Memory impairment	1	0	0	0
Mental impairment				
Learning difficulties	1	0	0	0
SYS ORGAN CLASS TOTAL:	486	1	0	0
Peripheral vascular disorders				
Arterial inflammatory diseases				
Allergic vasculitis	1	0	0	0
Vasculitis NOS	11	0	0	0
Peripheral ischaemia				
Peripheral ischaemia NOS	3	0	0	0
Raynaud's phenomenon	2	0	0	0
Vasospasm	5	0	0	0
Varicose veins (limbs)				
Varicose veins (without ulcer)	1	0	0	0
Vascular abnormalities of skin				
Vasodilatation	1	0	0	0
Venous disorders				
Vein thrombosis deep	1	0	0	0
Venous thrombophlebitis	4	0	0	0
SYS ORGAN CLASS TOTAL:	29	0	0	0
Pregnancy, puerperium & perinatal conditions				
Abortion & stillbirth				
Spontaneous abortion	2	0	0	0
Complications in pregnancy, labour & delivery				
Fetal distress syndrome	1	0	0	0
Pre-eclampsia	1	0	0	0
Pregnancy (all forms)				
Unintended pregnancy	2	0	0	0
Puerperal conditions				
Suppressed lactation	1	0	0	0
SYS ORGAN CLASS TOTAL:	7	0	0	0
Psychiatric disorders				
Affective disorders (all forms)				
Depression NOS	55	0	0	0
Depression aggravated	1	0	0	0
Endogenous depression	1	0	0	0
Mixed anxiety and depression	1	0	0	0
Mood swings	1	0	0	0
Miscellaneous psychiatric disorders				
Emotional instability	5	0	0	0
Personality disorder NOS	3	0	0	0
Neurotic disorders				
Anxiety neurosis	1	0	0	0
Dissociative disorder	2	0	0	0
Phobic disorder	1	0	0	0
Psychiatric symptoms & signs				
Abnormal behaviour NOS	4	0	0	0
Abnormal thinking	2	0	0	0
Aggression	14	0	0	0
Agitation	19	0	0	0
Anxiety	12	0	0	0
Apathy	1	0	0	0
Confusion	152	0	0	0
Delusion	4	0	0	0

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Depersonalisation	7	0	0	0
Disorientation	16	0	0	0
Euphoria	6	0	0	0
Exacerbation of anxiety	1	0	0	0
Formication	1	0	0	0
Hallucinations	69	0	0	0
Hallucinations aggravated	1	0	0	0
Mentation impaired	1	0	0	0
Mood alteration NOS	2	0	0	0
Nervousness	5	0	0	0
Panic reaction	1	0	0	0
Stammer	1	0	0	0
Psychoses (excluding affective psychoses)				
Paranoia	11	0	0	0
Paranoid psychosis	1	0	0	0
Psychosis NOS	9	0	0	0
Schizophrenia aggravated	2	0	0	0
Schizophreniform illness	2	0	0	0
Suicide & parasuicide				
Suicidal ideation	1	0	0	0
Suicide attempt	1	0	0	0
Drug dependence (all forms)				
Drug dependence NOS	2	0	0	0
SYS ORGAN CLASS TOTAL:	419	0	0	0
Renal & urinary disorders				
Nephritis, nephrotic syndrome & nephrosis				
Glomerulonephritis NOS	1	0	0	0
Nephritis interstitial	4	0	0	0
Nephrosis	1	0	0	0
Nephrotic syndrome	1	0	0	0
Renal vascular disorders				
Renal parenchymal haemorrhage	1	0	0	0
Urethral disorders				
Urethral disorder NOS	1	0	0	0
Urinary disease symptoms & signs				
Dysuria	8	0	0	0
Enuresis	1	0	0	0
Haematuria	6	0	0	0
Loin pain	2	0	0	0
Micturition disorder	1	0	0	0
Nocturia	2	0	0	0
Polyuria	2	0	0	0
Proteinuria	2	0	0	0
Renal pain	3	0	0	0
Strangury	1	0	0	0
Urinary frequency	8	0	0	0
Urinary incontinence	5	0	0	0
Urinary retention	4	0	0	0
Urine abnormal	10	0	0	0
Urine discolouration	1	0	0	0
Renal failure (all forms)				
Nephrotoxicity NOS	3	0	0	0
Renal failure NOS	8	1	0	0
Renal impairment NOS	1	0	0	0
Renal function disorders				
Blood urea increased	1	0	0	0
Renal & ureteral disorders NOS				
Toxic nephropathy	9	0	0	0
SYS ORGAN CLASS TOTAL:	87	1	0	0
Reproductive disorders				
Reproductive disorders NOS				
Libido decreased	21	0	0	0
Libido increased	1	0	0	0
Sexual dysfunction NOS	1	0	0	0
Miscellaneous breast disorders				
Breast engorgement	2	0	0	0
Breast enlargement	35	0	0	0
Breast lump NOS	2	0	0	0
Breast pain	66	0	0	0
Galactorrhoea	12	0	0	0
Gynaecomastia	144	0	0	0
Mastitis	11	0	0	0
Nipple disorder	6	0	0	0
Disorders of menstruation				
Amenorrhoea NOS	1	0	0	0
Dysmenorrhoea	1	0	0	0
Intermenstrual bleeding	1	0	0	0
Irregular menstrual cycle	3	0	0	0
Menorrhagia	2	0	0	0
Female reproductive tract infections				
Vaginal candidiasis	1	0	0	0
Vulvovaginitis	3	0	0	0
Menopausal & post-menopausal disorders				
Menopausal symptoms	1	0	0	0
Miscellaneous female reproductive tract disorders				
Vaginal haemorrhage	1	0	0	0
Male sexual disorders				
Erectile dysfunction	74	0	0	0
Scrotal & penile disorders				
Balanitis	1	0	0	0
Penile disorder NOS	2	0	0	0
Peyronie's disease	1	0	0	0
Testicular & epididymal disorders				
Testicular disorder NOS	3	0	0	0
Testicular pain	1	0	0	0
Testicular swelling	1	0	0	0
SYS ORGAN CLASS TOTAL:	398	0	0	0
Respiratory disorders				
Sudden infant death syndrome	1	1	0	0

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Respiratory symptoms & signs				
Chest tightness	24	0	0	0
Cough	7	0	0	0
Dyspnoea	52	0	0	0
Haemoptysis	2	0	0	0
Hyperventilation	2	0	0	0
Sore throat	2	0	0	0
Ventilatory disorders (exc foetal & neonatal)				
Respiratory failure (exc neonatal)	1	0	0	0
Lower respiratory tract infections				
Bronchopneumonia	3	1	0	0
Obstructive airways disorders				
Asthma	6	0	0	0
Bronchospasm	97	0	0	0
Bronchospasm aggravated	3	0	0	0
Bronchospasm in a known asthmatic	1	0	0	0
Chronic obstructive airways disease exacerbat	1	0	0	0
Exacerbation of asthma	14	0	0	0
Parenchymal lung disorders				
Alveolitis fibrosing	1	0	0	0
Pulmonary fibrosis	1	0	0	0
Laryngeal & tracheal disorders (exc infections)				
Laryngeal oedema	1	0	0	0
Laryngismus	1	0	0	0
Nasal cavity & sinus disorders (exc infections)				
Allergic rhinitis	1	0	0	0
Epistaxis	4	0	0	0
Nasal obstruction	2	0	0	0
Rhinitis NOS	4	0	0	0
Rhinorrhoea	1	0	0	0
Upper respiratory tract infections (all forms)				
Pharyngitis NOS	3	0	0	0
Sinusitis	1	0	0	0
SYS ORGAN CLASS TOTAL:	236	2	0	0
Skin & subcutaneous tissue disorders				
Application & injection site reactions				
Injection site inflammation	2	0	0	0
Injection site reaction	4	0	0	0
Bullous dermatoses				
Blister	12	0	0	0
Bullous dermatitis	6	0	0	0
Epidermal necrolysis	1	0	0	0
Erythema multiforme	25	0	0	0
Cornification & elastic tissue disorders				
Lichenification	1	0	0	0
Dermatitis & eczema				
Dermatitis NOS	10	0	0	0
Dermatitis lichenoid	5	0	0	0
Eczema NOS	17	0	0	0
Exfoliation NOS	5	0	0	0
Exfoliative dermatitis NOS	6	0	0	0
Localised exfoliation	6	0	0	0
Peri-oral dermatitis	1	0	0	0
Miscellaneous skin & subcutaneous tissue disorders				
Erythema nodosum	9	0	0	0
Pruritus	169	0	0	0
Scab	1	0	0	0
Skin disorder NOS	1	0	0	0
Skin nodule	1	0	0	0
Skin odour abnormal	1	0	0	0
Nail disorders				
Nail abnormality NOS	4	0	0	0
Onycholysis	1	0	0	0
Photosensitivity eruptions				
Photosensitivity reaction	42	0	0	0
Pigmentation disorders				
Pigmentation disorder NOS	1	0	0	0
Skin discolouration	1	0	0	0
Skin hyperpigmentation	1	0	0	0
Vitiligo	2	0	0	0
Rashes				
Allergic rash	4	0	0	0
Erythroderma	1	0	0	0
Localised skin reaction	3	0	0	0
Rash NOS	256	0	0	0
Rash erythematous	79	0	0	0
Rash follicular	1	0	0	0
Rash macular	7	0	0	0
Rash maculo-papular	62	0	0	0
Rash morbilliform	2	0	0	0
Rash papular	7	0	0	0
Rash psoriasiform	2	0	0	0
Rash pustular	4	0	0	0
Rash vesicular	6	0	0	0
Skin collagen vascular diseases				
Systemic lupus erythematosus rash	2	0	0	0
Skin ulcer & gangrene				
Leg ulcer (exc varicose)	1	0	0	0
Skin ulcer NOS	2	0	0	0
Sweating disorders				
Dyshidrosis	1	0	0	0
Night sweats	1	0	0	0
Sweating increased	27	0	0	0
Vascular abnormalities of skin				
Campbell de Morgan spots	1	0	0	0
Ecchymoses	7	0	0	0
Pallor	2	0	0	0
Petechiae	8	0	0	0
Purpura	20	0	0	0
Skin vasculitis NOS	2	0	0	0
Vasculitic rash	3	0	0	0
Angioedema				
Angioedema	49	0	0	0
Face oedema	79	0	0	0

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Giant urticaria	1	0	0	0
Periorbital oedema	29	0	0	0
Tongue oedema	12	0	0	0
Urticaria				
Dermatographia	2	0	0	0
Urticaria	228	0	0	0
Acne (all forms)				
Acne	1	0	0	0
Hair & hair follicle disorders				
Alopecia	46	0	0	0
Hair discolouration	1	0	0	0
Hair texture abnormal	1	0	0	0
Hypertrichosis	1	0	0	0
Sebaceous gland disorders				
Dry skin	4	0	0	0
Seborrhoea	2	0	0	0
Psoriasis & similar conditions				
Psoriasis aggravated	7	0	0	0
Skin & subcutaneous tissue bacterial infections				
Cellulitis	1	0	0	0
Skin & subcutaneous tissue viral infections				
Herpes simplex	3	0	0	0
SYS ORGAN CLASS TOTAL:	1313	0	0	0
TOTAL REACTIONS FOR DRUG:	5245	25	0	0

TOTAL REPORTS: 3,441 TOTAL FATAL OUTCOME: 25

Annex 7

APPENDIX 9

FAMOTIDINE (PEPCID 10 MG)
FOR NON-PRESCRIPTION USE:
SAFETY SUMMARY
01.01.95 to 31.08.99

Adverse Event By Body System Table
Famotidine Non-prescription Primary Reportable Marketed Reports 01/01/95 to 31/08/99

Body System	Term	Events	Serious	Non-serious
Body as a whole/site unspecified	Stools, formed	1	0	1
	Suntan irregular	1	0	1
	White spots, skin	1	0	1
	[Condition unspecified]	44	0	44
	Abdominal distention	45	0	45
	Abdominal pain	316	5	311
	Abdominal physical finding	2	0	2
	Abnormal feeling	15	0	15
	Accidental ingestion	12	3	9
	Alcohol intolerance	1	0	1
	Asthenia/fatigue	133	3	130
	Bacterial sepsis	1	1	0
	Bloated feeling	5	0	5
	Body ache	2	0	2
	Body as a whole/site unspecified condition	3	0	3
	Body fluid discoloration	1	0	1
	Body odour	4	0	4
	Burn	3	0	3
	Chest pain	94	1	93
	Chills	14	0	14
	Cold sensation	10	0	10
	Confusion	3	0	3
	Crying	1	0	1
	Dehydration	3	2	1
	Diaphragmatic hernia	2	0	2
	Dizziness	375	2	373
	Drug interaction	8	2	6
	Drug overdose	22	17	5
	Edema	81	3	78
	Fever	35	2	33
	Fluid retention	7	0	7
	Flushing	23	0	23
	Foreign body	1	0	1
	Fungal infection	6	0	6
	Hernia	1	0	1
	Hot flushes	11	0	11
	Influenza-like disease	7	0	7
	Intact medication in stool	2	0	2
	Irregular response	1	0	1
	Laboratory test abnormality	6	0	6
	Lack of response	1531	0	1531
	Loss of response	33	0	33
	Lower extremity edema	10	0	10
	Malaise	146	2	144
	Orthostatic dizziness	1	0	1
	Pain	40	0	40
	Pelvic pain	1	0	1
	Peripheral edema	3	0	3

Adverse Event By Body System Table
Famotidine Non-prescription Primary Reportable Marketed Reports 01/01/95 to 31/08/99 (cont'd)

Body System	Term	Events	Serious	Non-serious
Body as a whole/site unspecified (cont'd)	Peritonitis	2	2	0
	Presyncope	58	1	57
	Product abnormality	1	0	1
	Product confusion	1	0	1
	Product misuse	2	0	2
	Reaction	6	1	5
	Regional heaviness	1	0	1
	Sign/symptom	1	0	1
	Skin warm to touch	1	0	1
	Syncope	9	1	8
	Undissolved medication	1	0	1
	Upper extremity edema	11	0	11
	Upper respiratory infection	3	0	3
	Viral infection	2	0	2
	Warm sensation	8	0	8
	Total n° of episodes for body as a whole: 2981		45	
Cardiovascular system	Angina pectoris	2	0	2
	Arrhythmia	12	0	12
	Arterial disorder	1	0	1
	Atrial fibrillation	1	0	1
	Blood pressure decreased	4	0	4
	Blood pressure increased	63	0	63
	Bradycardia	2	0	2
	Cardiac arrest	1	1	0
	Cardiac disorder	1	0	1
	Cardiovascular disorder	2	1	1
	Ecchymosis	4	1	3
	Hemorrhage	2	0	2
	Hypertension	57	2	55
	Hypotension	12	0	12
	Irregular heartbeat	11	1	10
	Mitral valve prolapse	1	0	1
	Myocardial infarction	5	5	0
	Orthostatic hypotension	1	0	1
	Palpitation	52	0	52
	Peripheral ischemia	2	0	2
	Peripheral vascular disorder	8	0	8
	Petechia	1	0	1
	Skipped heartbeat	2	0	2
	Tachycardia	62	0	62
	Thrombosis	1	0	1
	Transient ischemic attack	1	0	1
	Vascular disorder	1	0	1
	Vascular rupture	2	0	2
	Vasodilatation	7	0	7
	Total n° of episodes for cardiovascular system: 304		11	

Adverse Event By Body System Table
Famotidine Non-prescription Primary Reportable Marketed Reports 01/01/95 to 31/08/99 (cont'd)

Body System	Term	Events	Serious	Non-serious
Digestive system	Acid reflux	4	0	4
	Anorectal disorder	1	0	1
	Anorectal hemorrhage	11	3	11
	Aphthous stomatitis	1	0	1
	Bowel movement pattern change	41	0	41
	Bowel sound abnormality	4	0	4
	Colitis	1	1	0
	Constipation	582	1	581
	Dark stool	123	0	123
	Deglutition disorder	33	0	33
	Dental disorder	1	0	1
	Diarrhea	949	3	946
	Digestive gas symptoms	147	0	147
	Dry mouth	337	0	337
	Dyschezia	1	0	1
	Dysentery	1	0	1
	Dysgeusia	72	0	72
	Dyspepsia	98	1	98
	Epigastric discomfort	92	1	91
	Esophagalgia	2	0	2
	Esophageal disorder	1	0	1
	Esophageal dyskinesia	1	0	1
	Esophageal obstruction	1	0	1
	Esophageal tear	1	0	1
	Esophagitis	5	0	5
	Fecal abnormality	83	0	83
	Fecal impaction	6	0	6
	Fecal incontinence	1	0	1
	Fecal occult blood	1	0	1
	Flatulence	62	0	62
	Functional intestinal disorder	2	0	2
	Gastric acid decreased	1	0	1
	Gastric dilatation	3	0	3
	Gastric disorder	57	0	57
	Gastritis	7	0	7
	Gastrooesophageal reflux disease	1	0	1
	Gastrointestinal bleeding	8	2	6
	Gastrointestinal disorder	2	0	2
	Gingival disorder	2	0	2
	Gingival hemorrhage	1	0	1
	Gingival hyperplasia	1	0	1
	Gingivitis	2	0	2
	Glossitis	6	0	6
	Glossodynia	14	0	14
	Heartburn	87	0	87
	Hematochezia	10	0	10
	Hemorrhagic peptic ulcer	1	1	0
	Hemorrhoids	6	0	6
	Intestinal diverticulitis	1	1	0
	Intestinal diverticulum	1	0	1

Adverse Event By Body System Table
Famotidine Non-prescription Primary Reportable Marketed Reports 01/01/95 to 31/08/99 (cont'd)

Body System	Term	Events	Serious	Non-serious
Digestive system (cont'd)	Intestinal malabsorption	1	0	1
	Intestinal obstruction	2	2	0
	Intestinal vascular insufficiency	1	1	0
	Irritable bowel syndrome	2	2	0
	Lip disorder	31	1	30
	Lip dryness	5	0	5
	Melena	6	1	5
	Nausea	410	1	409
	Oral candidiasis	2	0	2
	Oral discoloration	1	0	1
	Oral disorder	1	0	1
	Oral infection	1	0	1
	Oral lesion	12	0	12
	Oral leukoplakia	1	0	1
	Oral pain	3	0	3
	Oral ulcer	4	0	4
	Pancreatitis	1	1	0
	Peptic ulcer	1	0	1
	Rectal discharge	2	0	2
	Rectal disorder	1	0	1
	Saliva altered	3	0	3
	Salivation increased	18	0	18
	Stomatitis	13	0	13
	Taste disorder	2	0	2
	Taste loss	7	0	7
	Tongue discoloration	13	0	13
	Tongue disorder	15	4	11
	Tongue edema	2	1	1
	Tongue lesion	1	0	1
	Vomiting	157	1	156
	Total n° of episodes for digestive system: 3072		29	
Endocrine system	Loss of diabetic control	5	0	5
	Total n° of episodes for endocrine system: 5			
Eyes, ears, nose and throat	Accommodation disorder	1	0	1
	Amblyopia	3	0	3
	Blepharal disorder	6	0	6
	Blepharal edema	5	0	5
	Blurred vision	17	0	17
	Conjunctival injection	3	0	3
	Conjuntivitis	1	0	1
	Diplopia	6	0	6
	Dry eyes	10	0	10
	Dry nose	5	0	5
	Dry throat	12	0	12
	Epistaxis	22	0	22
	External otic obstruction	2	0	2
	Intraocular pressure increased	2	0	2
	Laryngeal spasm	4	1	3
	Mydriasis	1	0	1
	Nasal congestion	4	0	4
	Nasal discomfort	2	0	2

Adverse Event By Body System Table
Famotidine Non-prescription Primary Reportable Marketed Reports 01/01/95 to 31/08/99 (cont'd)

Body System	Term	Events	Serious	Non-serious
Ears, eyes, nose and throat (cont'd)	Ocular hypotension	1	0	1
	Olfactory disorder	3	0	3
	Ophthalmic burning	3	0	3
	Ophthalmic discharge	1	0	1
	Ophthalmic disorder	6	0	6
	Ophthalmic edema	1	0	1
	Ophthalmic hemorrhage	2	0	2
	Ophthalmic inflammation	1	0	1
	Ophthalmic irritation	1	0	1
	Ophthalmic itching	8	0	8
	Ophthalmic pain	3	0	3
	Otic congestion	1	0	1
	Otic disorder	2	0	2
	Otic pain	2	0	2
	Otic swelling	1	0	1
	Pharyngeal disorder	1	0	1
	Pharyngeal edema	4	2	2
	Pharyngitis	80	0	80
	Photophobia	1	0	1
	Photopsia	3	0	3
	Ptosis	1	0	1
	Sinus disorder	7	0	7
	Sinusitis	3	0	3
	Throat tightness	1	0	1
	Tinnitus	45	0	45
	Tonsillitis	1	0	1
	Tunnel vision	1	0	1
	Visual disturbance	7	0	7
	Visual field defect	1	0	1
	Visual loss	2	0	2
	Vitreous degeneration	1	0	1
	Vitreous opacity	1	0	1
	Vocal disturbance	4	1	3
	Total n° of episodes for ears, eyes, nose and throat: 293 (4)			
Hemic and lymphatic system	Anemia	5	0	1
	Erythrocytes decreased	3	0	3
	Hematocrit decreased	1	0	1
	Hematologic disorder	1	0	1
	Hemoglobin decreased	1	0	1
	Hemolytic anemia	1	1	0
	Leukocytes decreased	2	0	2
	Leukopenia	2	0	2
	Microcytic anaemia	1	0	1
	Prothrombin time increased	7	1	6
	Thrombocytopenia	1	0	1
	Total n° of episodes for hemic and lymphatic system: 23 (2)			

Adverse Event By Body System Table
Famotidine Non-prescription Primary Reportable Marketed Reports 01/01/95 to 31/08/99 (cont'd)

Body System	Term	Events	Serious	Non-serious
Hepatobiliary system	Biliary pain	1	0	1
	Cholecystitis	1	0	1
	Cholestasis	2	0	2
	Fatty liver	1	0	1
	Hepatic disorder	2	1	1
	Hepatic function abnormality	8	0	8
	Hepatic tenderness	2	0	2
	Hepatitis	2	0	2
	Jaundice	4	0	4
	Total n° of episodes for hepatobiliary system: 17		(1)	
Immune system	Allergy	1	0	1
	Anaphylactoid reaction	1	0	1
	Anaphylaxis	1	1	0
	Angioedema	3	2	1
	Drug allergy	2	1	1
	Hypersensitivity reaction	15	4	11
	Total n° of episodes for immune system: 22		(8)	
Metabolism and nutrition	Alanine aminotransferase increased	2	0	2
	Alkaline phosphatase increased	2	0	2
	Anorexia	24	0	24
	Appetite change	7	0	7
	Appetite increased	14	0	14
	Aspartate aminotransferase increased	2	0	2
	Blood protein disorder	1	0	1
	Dietary control	1	0	1
	Gamma-glutamyl transpeptidase increased	2	0	2
	Hypercholesterolemia	3	0	3
	Hyperglycemia	27	0	27
	Hypertriglyceridemia	1	0	1
	Hyperuricemia	2	0	2
	Hypoglycemia	5	0	5
	Serum iron increased	1	0	1
	Thirst increased	36	0	36
	Weight gain	16	0	16
	Weight loss	20	2	18
	Total n° of episodes for metabolism and nutrition: 153		(2)	

Adverse Event By Body System Table
Famotidine Non-prescription Primary Reportable Marketed Reports 01/01/95 to 31/08/99 (cont'd)

Body System	Term	Events	Serious	Non-serious
Musculoskeletal system	Ankle pain	2	0	2
	Arm pain	4	1	3
	Arthralgia	27	0	27
	Arthritis	6	0	6
	Articular disorder	4	0	4
	Back pain	38	0	38
	Bone pain	1	0	1
	Foot pain	3	0	3
	Gout	4	0	4
	Hand pain	3	0	3
	Hip pain	1	0	1
	Joint swelling	13	0	13
	Knee pain	5	0	5
	Leg pain	9	0	9
	Mandibular pain	4	0	4
	Muscular cramp	45	0	45
	Muscular disorder	5	0	5
	Muscular swelling	1	0	1
	Muscular weakness	11	0	11
	Musculoskeletal chest pain	2	0	2
	Musculoskeletal condition	1	0	1
	Musculoskeletal pain	1	0	1
	Musculoskeletal stiffness	6	0	6
	Myalgia	26	0	26
	Neck swelling	1	1	0
	Range of motion decreased	4	0	4
	Rheumatoid arthritis	1	0	1
	Shoulder pain	3	0	3
	Wrist pain	1	0	1
	Total n° of episodes for musculoskeletal: 215		(2)	
Nervous system	Akathisia	15	0	15
	Aphasia	2	0	2
	Ataxia	2	0	2
	Balance disturbance	6	0	6
	Central nervous system disorder	1	0	1
	Dream abnormality	15	0	15
	Extrapyramidal symptom	1	0	1
	Falling	1	0	1
	Gait abnormality	6	1	5
	Grand mal seizure	2	1	1
	Headache	416	0	416
	Hyperkinesia	3	0	3
	Hypertonia	3	0	3
	Hypersthesia	33	0	33
	Insomnia	200	0	200
	Migraine	12	0	12
	Movement disorder	1	0	1
	Muscular spasm	9	0	9
	Paresthesia	74	1	73
	Seizure	2	1	1

Adverse Event By Body System Table
Famotidine Non-prescription Primary Reportable Marketed Reports 01/01/95 to 31/08/99 (cont'd)

Body System	Term	Events	Serious	Non-serious
Nervous system (cont'd)	Sleep disorder	9	0	9
	Somnolence	159	0	159
	Speech disorder	3	0	3
	Stupor	2	0	2
	Tongue movement abnormality	1	0	1
	Tremor	25	0	25
	Unsteady movement	3	0	3
	Vertigo	11	0	11
	Total n° of episodes for nervous system: 960		(4)	
Psychiatric disorder	Aggressive behaviour	2	0	2
	Agitation	7	0	7
	Anxiety	36	0	36
	Anxiety disorder	5	0	5
	Bipolar disorder	1	0	1
	Confusion	21	1	20
	Depersonalisation	1	1	0
	Depression	34	1	33
	Disorientation	9	1	8
	Eating disorder	1	0	1
	Emotional lability	3	0	3
	Excitement	4	0	4
	Hallucination	14	3	11
	Intoxicated feeling	3	0	3
	Irritability	7	0	7
	Memory impairment	7	0	7
	Mental acuity decreased	19	0	19
	Mental state	1	0	1
	Nervousness	109	0	109
	Panic disorder	2	0	2
	Personality change	2	0	2
	Psychosis	1	0	1
	Tranquility	1	0	1
	Total n° of episodes for psychiatric disorders: 248		(7)	
Respiratory system	Asthma	3	0	3
	Breathing pattern abnormality	2	0	2
	Bronchitis	1	0	1
	Choking	2	0	2
	Cough	24	0	24
	Dyspnea	79	3	76
	Halitosis	6	0	6
	Hemoptysis	11	0	11
	Hiccups	6	0	6
	Hyperventilation	1	0	1
	Hypoventilation	1	0	1
	Pulmonary congestion	1	0	1
	Respiratory condition	1	0	1
	Respiratory distress	11	0	11
	Sneezing	2	0	2
	Sputum altered	4	0	4
	Wheezing	1	0	1
	Total n° of episodes for respiratory: 149		(3)	

Adverse Event By Body System Table
Famotidine Non-prescription Primary Reportable Marketed Reports 01/01/95 to 31/08/99 (cont'd)

Body System	Term	Events	Serious	Non-serious
Skin and skin appendages	Acne	11	0	11
	Alopecia	88	0	88
	Anogenital pruritus	4	0	4
	Blister	5	0	5
	Contact dermatitis	1	0	1
	Cutaneous fungal disease	1	0	1
	Desquamation	1	0	1
	Fixed drug eruption	1	0	1
	Furuncle	1	0	1
	Herpes simplex	4	0	4
	Herpes zoster	1	0	1
	Hypermelanosis	1	0	1
	Ichthyosis	6	0	6
	Nail unit disorder	2	0	2
	Night sweats	2	0	2
	Nonspecific hair disorder	5	0	5
	Nonspecific skin disorder	4	0	4
	Pallor	20	0	20
	Perspiration	20	0	20
	Photosensitivity	1	0	1
	Pigmentary disorder	2	0	2
	Pruritus	318	2	316
	Psoriasis vulgaris	2	0	2
	Rash	361	5	356
	Skin erythema	10	0	10
	Skin infection	1	0	1
	Skin or skin appendage cond.	2	0	2
	Sweat gland disorder	33	0	33
	Urticaria	131	2	129
	Vesiculobullous rash	5	0	5
	Xerosis	8	0	8
	Total n° of episodes for skin & skin appendages: 846 (-1)			
Urogenital system	Balanitis	1	0	1
	Bladder dysfunction	2	0	2
	Bladder pain	1	0	1
	Breast atrophy	1	0	1
	Breast disorder	1	0	1
	Breast enlargement	4	0	4
	Breast pain	13	0	13
	Cystitis	5	0	5
	Dysuria	34	0	34
	Ejaculation function disorder	1	0	1
	Erectile dysfunction	1	0	1
	Gynaecomastia	6	0	6
	Hematuria	8	0	8
	Impotence	30	0	1
	Libido decreased	12	0	12
	Menstrual disorder	8	0	8
	Nocturia	7	0	7
	Oliguria	6	0	6
	Orgasmic dysfunction	1	0	1

Adverse Event By Body System Table
Famotidine Non-prescription Primary Reportable Marketed Reports 01/01/95 to 31/08/99 (cont'd)

Body System	Term	Events	Serious	Non-serious
Urogenital system (cont'd)	Polyuria	12	0	12
	Product use during pregnancy	8	0	8
	Prostatic disorder	6	0	6
	Renal disorder	1	0	1
	Renal pain	6	0	6
	Sexual dysfunction	5	0	5
	Upper urinary tract infection	1	0	1
	Urinary frequency	62	0	62
	Urinary hesitancy	3	0	3
	Urinary incontinence	7	0	7
	Urinary retention	1	0	1
	Urinary tract infection	5	0	5
	Urinary urgency	4	0	4
	Urination disorder	4	0	4
	Urine abnormality	33	2	31
	Urolithiasis	2	0	2
	Uterine hemorrhage	5	0	5
	Vaginal dryness	1	0	1
	Vaginal hemorrhage	3	0	3
	Vaginal pruritus	5	0	5
	Vaginal swelling	1	0	1
	Vaginitis	7	0	7
	Total n° of episodes for urogential system: 296 (2)			
Total number of episodes: 9584				

Annex 8

HEARTBURN AND GASTRO-OESOPHAGEAL REFLUX

J R BENNETT, MD. Consultant Physician, Hull Royal Infirmary, Hull.

SUMMARY Heartburn is a readily recognised symptom which half the British population have experienced at some time, and a fifth have frequently. It is the predominant symptom of gastro-oesophageal reflux, although less than two thirds of sufferers have endoscopically visible oesophagitis. Heartburn can also be associated with peptic ulcers or functional dyspepsia.

Several changes in oesophageal function contribute to the syndrome of gastro-oesophageal reflux, the most important being inadequacy of the complex mechanism at the gastro-oesophageal junction. Understanding the various functional failures offers a better understanding of the therapeutic possibilities.

Heartburn (pyrosis) is a mucosal irritation which is caused by refluxed gastric juice. Discomfort or pain, usually burning in character, is felt behind the sternum, often appearing to rise from the epigastrium towards or into the throat, sometimes radiating into the back. Occasionally, although the pain arises in the lower oesophagus, it may be experienced entirely in the throat or in the epigastrium. It is an intermittent symptom, particularly occurring within 30 minutes of meals, on exercise, after bending, or on lying down; it may waken patients from sleep. A large meal, especially if it contains fat, chocolate, coffee or alcohol, is particularly likely to precipitate heartburn. The discomfort often disappears quickly on drinking water or milk, or after taking an antacid. If heartburn occurs frequently it can interfere with the patient's way of life, particularly work or pleasure involving lying down or bending, such as gardening and sexual intercourse. However, it is so common that its occasional appearance can hardly be considered pathological.

About 50% of people in Britain have had heartburn at some time. Of the 40% of the population who experienced dyspepsia in a six-month period, more than half had heartburn (Figure 1).[1] (Only a quarter of British patients with dyspepsia consult their general practitioner.) However, heartburn is not synonymous with gastro-oesophageal reflux; it may be a symptom of other pathology (eg, peptic ulceration) or of non-organic disease such as functional dyspepsia.

Heartburn occurs in about two thirds of all pregnant women, especially in the second and third trimesters.

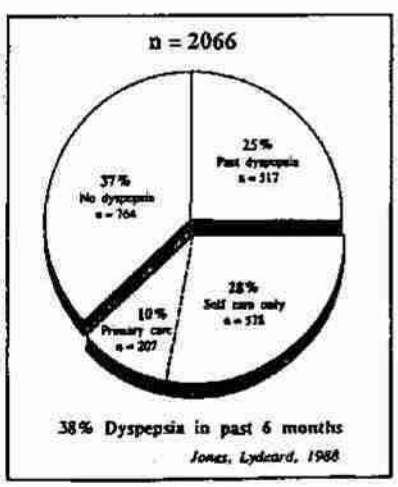


Figure 1. The elements in the normal gastro-oesophageal barrier which prevent the reflux of gastric juice

Other oesophageal pain

The oesophagus may give rise to pain of any character, but is often described as 'gripping' or 'knife-like'. The pain is usually central sternal in origin but may radiate widely to the abdomen, back, neck and arms. It can be severe, simulating cardiac, biliary or duodenal pain. As many as one third of patients admitted to hospital with a provisional diagnosis of cardiac pain may turn out only to have oesophageal disease.[2] Sometimes oesophageal pain is experienced entirely in the epigastrium, when it may mimic peptic ulceration.

Odynophagia

This term describes a transitory discomfort, usually of burning character, felt behind the sternum when food or fluid (usually a hot or alcoholic drink, or citrus juice) is swallowed. It is characteristic and diagnostic of oesophagitis, occurring both in reflux disease and infective oesophagitis.

The cause of heartburn

Heartburn is the commonest and main symptom of gastro-oesophageal reflux disease. Gastro-oesophageal reflux may exist for years without symptoms and the severity of symptoms is a poor guide to the degree of reflux. Many patients first present with a stricture, an oesophageal ulcer, or a columnar-lined Barrett's oesophagus (all considered complications of chronic reflux), having had no preceding reflux symptoms. However, reflux usually causes heartburn in the majority of patients.

ADDRESS CORRESPONDENCE TO Dr John Bennett, Consultant Physician, Hull Royal Infirmary, Anlaby Road, Hull.

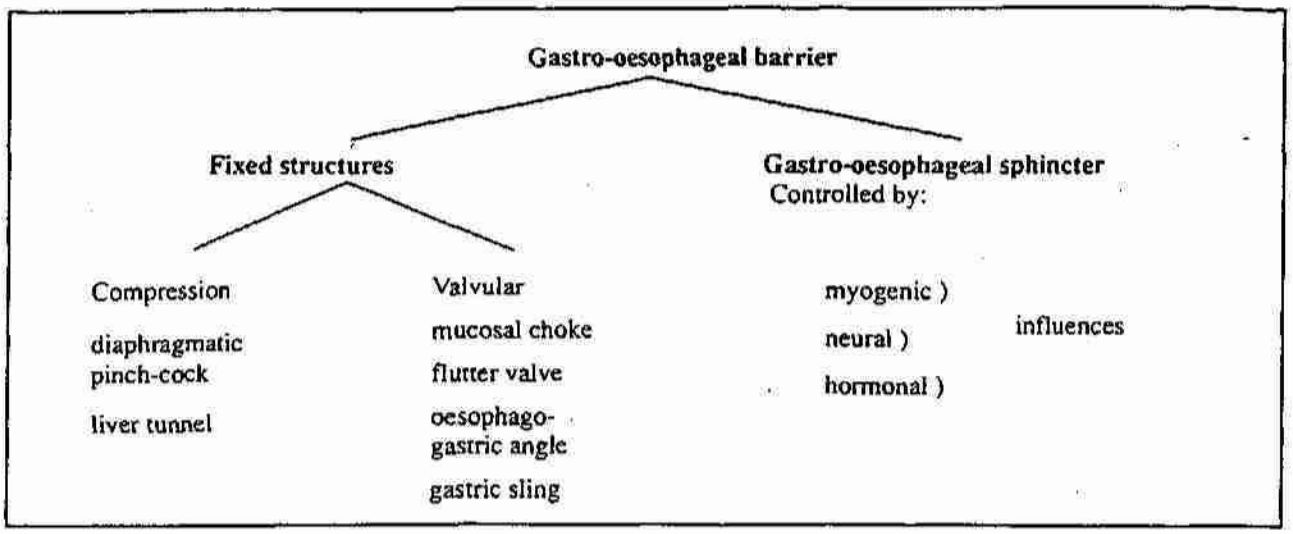


Figure 2.

DIFFERENTIAL DIAGNOSIS

Peptic ulcer

Gastro-oesophageal reflux often complicates, or co-exists with, peptic ulceration, probably because of changes in gastric motility and gastro-oesophageal sphincter dysfunction, and a higher acid content of the gastric juice.[3,4] A peptic ulcer should be sought radiologically or endoscopically in most patients with reflux symptoms as an ulcer modifies the management approach.

Functional dyspepsia

The syndrome of functional dyspepsia embraces a number of symptoms, including upper abdominal fullness, nausea, early satiety, anorexia, morning vomiting, belching, and also heartburn. These symptoms occur because of disordered gastric motility with delayed gastric emptying, duodenogastric motility with delayed gastric emptying, and perhaps duodenogastric reflux. Although the heartburn may partly respond to anti-reflux measures, the other symptoms will not. Anti-reflux surgery should be avoided in such patients, for they respond poorly. Prokinetic agents, such as metoclopramide and cisapride, may be more helpful.

MECHANISM OF GASTRO-OESOPHAGEAL REFLUX

Reflux of gastric juice into the oesophagus is normally prevented by barrier mechanisms, which include the anatomical arrangements at the diaphragmatic oesophageal hiatus, and the lower oesophageal sphincter (gastro-oesophageal sphincter) (Figure 2). The barrier mechanism is necessarily incomplete as it has, at least, to allow belching and vomiting. Reflux of gastric contents across the barrier into the lower oesophagus occurs in everyone several times a day due to transient relaxations of the gastro-oesophageal sphincter, the errant juices being quickly returned to the stomach by gravity, primary peristalsis induced by swallowing, or secondary peristalsis triggered by oesophageal distension. To produce symptoms or oesophagitis (or both) other factors must be involved. Compared with normal subjects, patients with reflux oesophagitis may have:

- more frequent episodes of reflux;
- abnormalities of gastric function;
- slower oesophageal emptying ('reduced clearance');
- more irritant juice;
- diminished mucosal resistance.

Frequency of reflux

The elements in the normal barrier which prevent reflux are shown in Figure 2. It is impossible to determine the contribution of each fixed structure, but in some patients deficiency of one or more may be a major contribution to reflux.

The gastro-oesophageal sphincter is a band of specialised muscle squeezing the oesophageal lumen. Several factors, especially hormones, have been shown to affect sphincter tone. Those which may contribute causatively to reflux oesophagitis are shown in Table 1. The strength of the sphincter is sufficient to keep the sphincter segment narrow and resist opening force from below.

It was believed that reflux always forced its way through a weak sphincter, but in fact the sphincter frequently relaxes transiently, not in response to a swallow.[5] Although the mechanism of these transient relaxations is not known, they seem to account for the episodes of diurnal reflux seen in normal subjects, and for much of the reflux in patients with symptomatic reflux disease.

Hiatus hernia

Early descriptions of gastro-oesophageal reflux stressed its relationship with herniation of the stomach through the

Table 1. Factors diminishing gastro-oesophageal sphincter tone and increasing reflux

Myogenic
Oesophagitis
Systemic sclerosis
After achalasia therapy
Neural
Oesophagitis
Early systemic sclerosis
Smoking
Alcohol
Hormonal
Menstruation
Pregnancy
Fat/chocolate eating
Coffee

oesophageal hiatus of the diaphragm. A hiatus hernia may be produced transiently in most normal individuals, and such herniation is part of the normal vomiting mechanism, so it is not a useful diagnostic finding. A fixed hiatus hernia could possibly play a part in the pathogenesis of reflux disease (perhaps by delaying oesophageal clearance[6]), but is not the most important causative factor and the radiological demonstration of one is not a sensitive or specific way to confirm a diagnosis of reflux disease. Moreover, patients often become unnecessarily perturbed when they are told they 'have a hiatus hernia', believing it likely to be subjected to the same hazards and complications as inguinal or femoral herniae, and to require surgical treatment. It would be desirable if the term 'hiatus hernia' ceased to be used as a diagnostic label in patients with reflux symptoms.

Gastric factors

Potentially, three abnormalities of gastric function could contribute to gastro-oesophageal reflux disease:

- gastric secretion;
- gastric emptying;
- duodenogastric reflux.

Gastric secretion is usually similar to that in normal subjects, though subtle differences have been detected. Gastric emptying may be slower, especially for solids, in some patients with gastro-oesophageal reflux.[7]

Duodenogastric reflux may occur more commonly in patients with reflux oesophagitis.[8]

Oesophageal clearance

The oesophagus deals with refluxed, acidic juice in two different ways. Most of it is returned to the stomach by peristalsis, which may be primary (induced by a swallow) or secondary (induced by oesophageal stimulation by the refluxed material).[9] In conditions such as systemic sclerosis, when peristalsis is lost, the oesophagus loses this clearing action and becomes very vulnerable to reflux and the development of oesophagitis. With increasing degrees of oesophagitis the proportion of ineffective or non-propagated peristaltic waves increases greatly.[10] This phenomenon is one element in the tendency of reflux disease to be self-perpetuating.

The second, and auxiliary, method of disposing of acid is neutralisation by swallowed alkaline saliva.[11] Salivary secretion increases during heartburn and stimulated saliva has a greater neutralising capacity.

Composition of refluxed juice

The constituents of refluxed juice chiefly responsible for epithelial damage are acid, pepsin and perhaps bile; the contribution of pancreatic enzymes is uncertain. Oesophagitis may occur in achlorhydric subjects, or even after total gastrectomy, but in most patients acid and pepsin are the important factors. Although major differences in gastric acid secretion have not been clearly shown in reflux subjects, subtle increases in acid concentration may determine the severity of reflux disease.[12]

Studies of bile salt concentrations in oesophageal fluid have yielded conflicting results. If present at all, concentrations are low, though even small amounts could have a deleterious effect on mucosal permeability.[13]

Mucosal sensitivity (tissue resistance)

Oesophageal mucosal defences may be considered as pre-epithelial, epithelial and post-epithelial.[14]

Pre-epithelial defences. These include the unstirred mucus layer, mainly derived from swallowed saliva, but partly also from submucous glands.

Epithelial defences. The intercellular junctions of the stratum granulosum resist acid attack until a late stage in the inflammatory process. Beneath this, the prickle cell layer contains sodium/potassium ATPase which maintains cellular integrity. H+ion penetration reduces this enzyme's activity and causes cell swelling and rupture.

Post-epithelial defences. These depend on blood flow, dispersing H+ ions and delivering $HCO_3$1 ions.

DIAGNOSIS OF GASTRO-OESOPHAGEAL REFLUX

In many patients the diagnosis is easy. The patient complains of heartburn, with characteristic postural and dietary associations, without dysphagia, vomiting or weight loss. In such individuals, tests are unnecessary, though follow-up is desirable to ensure that appropriate therapy has given relief, and that no new symptom has arisen.

If the symptoms arise unexpectedly, are less typical, are associated with epigastric pain or dysphagia, or if typical symptoms fail to respond to treatment, then *upper gastrointestinal endoscopy* is desirable, not only to try and confirm reflux oesophagitis but also particularly to discover a peptic ulcer or carcinoma of cardia or pylorus which may cause reflux symptoms.

If chest pain is less typically oesophageal, especially if it resembles cardiac pain, more careful assessment is needed, using tests to provoke oesophageal pain.

INVESTIGATIONS IN GASTRO-OESOPHAGEAL REFLUX

Reflux symptoms may be present without oesophagitis; reflux oesophagitis may not cause symptoms; and pathological reflux may exist without oesophagitis or symptoms. Tests must, therefore, be categorised as to precisely what abnormalities they demonstrate.

TESTS FOR REFLUX[15]

Barium radiology remains insensitive and unreliable as a test for gastro-oesophageal reflux. Scintiscanning gives a semi-quantitative measure of reflux but it is cumbersome, uncomfortable and involves radioactivity.

Intraluminal pH measurement

Although acid is not the entire cause of reflux disease, acid does reflux abnormally frequently in the great majority of patients with the disorder. Measuring the frequency with which acid enters the lower oesophagus using a small pH electrode is a relatively simple way of quantifying at least the frequency of reflux. Careful attention to detail (eg, positioning of the electrode) is essential if the results are to be useful and reliable.

Oesophageal pH can be monitored continuously over 12 to 24 hours, using a solid state recorder with subsequent computerised play-back and analysis.

Complicated 'scores' are probably unnecessary for interpretation. The percentage time below pH 4 is the single best criterion and this is normally up to 5% over 24 hours.

However, the 'normal' is age-related, and over 45 years 'normal' may be higher.

TESTS FOR OESOPHAGITIS (AND TO EXCLUDE OTHER PATHOLOGY)

Barium swallow and meal

A barium meal is insensitive and poorly specific in diagnosing mucosal inflammation, but will usually detect or exclude alternative pathology such as peptic ulceration or malignancy, and will usually detect motility abnormalities of the oesophagus.

Fibre-optic upper gastro-intestinal endoscopy

Although more uncomfortable, and slightly more hazardous to the patient, endoscopy gives more information about oesophageal disease than does radiology. It will detect ulcers and carcinoma at least as well, but also enables an accurate assessment of oesophagitis, and permits mucosal biopsies. Description and grading of oesophagitis is still contentious: for a clear review see Armstrong *et al.*[16]

About a third of patients with gastro-oesophageal reflux will have no detectable oesophagitis. The severity of oesophagitis correlates with the degree of reflux, but symptoms are not proportional to mucosal change and severe symptoms occur in patients with no oesophagitis, while advanced mucosal disease is sometimes discovered in individuals with few symptoms.

Oesophageal biopsy

Of the 30% of patients who do not have endoscopically visible oesophagitis some have histological abnormalities in mucosal biopsies. Conventional histological changes of inflammation are not always present, but hyperplasia of the basal cell layers of the squamous mucosa, with elongation of papillae towards the surface, is characteristic.[17]

TESTS FOR OESOPHAGEAL PAIN

Oesophageal perfusion

In almost all patients with pain from reflux oesophagitis the discomfort can be precipitated or reproduced by dripping 0.1 N hydrochloric acid into the oesophagus in a 'single-blind' manner, using saline as a control. The patient compares any induced discomfort with his spontaneous pain.[18]

OTHER TESTS

Oesophageal manometry

Pressure recording in the oesophagus permits the measurement of lower oesophageal sphincter tone, and assessment of oesophageal peristalsis. However, it is of small value in the *diagnosis* of gastro-oesophageal reflux because, although gastro-oesophageal sphincter tone tends to be lower in reflux subjects, there is considerable overlap with the normal population. Manometry is desirable as a preliminary to surgery in patients who respond poorly to medical treatment, to assess oesophageal peristalsis and sphincter tone, and it will also detect aperistalsis (as in systemic sclerosis). It may detect motor abnormalities, such as diffuse oesophageal spasm, which may themselves cause oesophageal pain in the absence of gastro-oesophageal reflux, or spasm associated with reflux.

MANAGEMENT OF GASTRO-OESOPHAGEAL REFLUX

Many people who experience intermittent heartburn find quick relief from any antacid preparation. Others require more treatment, and although the various available therapies may be tried empirically, it is helpful to consider their modes of action. As reflux oesophagitis is usually caused by a number of interacting abnormalities so treatment may be directed at one or other of those factors.[19]

Frequency of reflux. Certain foods reduce lower oesophageal sphincter tone and should be avoided - particularly fat, chocolate, coffee, alcohol and spices. Cigarette smoking weakens the sphincter and allows reflux, so should be stopped.

The lower oesophageal sphincter may be strengthened by prokinetic drugs, of which cisapride is currently the most effective. However, reflux is frequently not due to weakness of the resting sphincter, but rather to its inappropriate relaxation (especially during sleep), and at present this is not susceptible to pharmacological control.

Compounds containing sodium alginate and antacid interact with gastric acid to produce a floating, viscous foam which diminishes the frequency and duration of acid reflux.

Surgical anti-reflux operations markedly diminish reflux.

Gastric factors. The volume of gastric contents should be kept small by avoiding large meals. Gastric emptying may be accelerated by a prokinetic such as metoclopramide or cisapride. Gastric secretory volume is lowered by anti-secretory drugs like histamine H2 antagonists or proton-pump inhibitors.

Oesophageal clearing. Any refluxed juice should be cleared from the oesophagus as quickly as possible to shorten contact with the mucosa. Swallowing induces primary peristalsis and is encouraged by antacids given as chewable tablets, which also stimulate secretion of alkaline saliva. At night, propping up the bed-head by 20 cm reduces acid contact time and improves symptoms and oesophagitis.

Constituents of refluxed juice. The acid content can be neutralised by antacids, or reduced by histamine H_2 antagonists or proton pump inhibitors. At present no effective agent is available to lower concentration of pepsin or bile salts, although the amount of duodeno-gastric reflux of bile may be lessened by prokinetic agents.

Mucosal sensitivity. Drugs, such as corticosteroids or non-steroidal anti-inflammatory agents may be particularly irritant to the oesophagus and should be stopped if possible, or reduced to the minimum practicable dose. Local anaesthetic agents have not been shown to diminish mucosal pain-sensitivity. Cigarette smoke diminishes mucosal resistance to H+ ion penetration and so do drugs, including antibiotics and non-steroidal anti-inflammatory drugs. Carbenoxolone increases mucosal repair mechan-

ıms, but has not been widely used, partly because of its aldosterone-like side-effects. Sucralfate enhances resistance of the mucosa to acid, pepsin and bile, though its erformance in clinical trials has not been uniformly good.

′icious circles?

Improving the oesophagitis, by whatever means, may itself e helpful in controlling gastro-oesophageal reflux. Experimental studies have shown that oesophagitis weakens e lower oesophageal sphincter, a reversible effect. Oesophagitis diminishes oesophageal acid clearing, which improves after medical treatment. The inflamed oesophagus : more pain-sensitive and has increased permeability to hydrogen ions. Thus, if a period of intensive treatment can improve the condition, relapse is not inevitable when treatıent is partially or wholly withdrawn.

A PRACTICAL APPROACH TO TREATMENT[19]

ife-style modification

ny excess weight should be removed. This is a most effective therapeutic step, although the mechanism is un-ertain. Smoking should stop, and fat, chocolate, alcohol id coffee should be discouraged. Meals should be small .. lume and not taken late at night. Drugs which may aggravate the condition (non-steroidal anti-inflamatories, anti-cholinergics, calcium-channel blockers and eophylline compounds) should be stopped or at least reduced, if possible.

ıitial medication

n antacid-aliginate compound is prescribed after meals and at bed-time, supplemented by antacid tablets sucked equently (every one to two hours between meals).

Further medication

symptoms are more severe, or persist, a histamine H2 ocking drug may be given. The standard dose (as for ptic ulcers) may suffice, but often higher and more frequent doses (eg, cimetidine 400 mg qds, ranitidine 300 g bd, famotidine 40 mg bd) are needed.

ı response is still inadequate the bed-head should be levated on 20 cm blocks, or a prokinetic (eg, cisapride g before meals and at bed-time) added.

The proton-pump inhibitor omeprazole (40 mg with breakfast or 20 mg twice-daily) give a high rate of symptom reduction and healing of oesophagitis. At present it is only recommended for courses of eight weeks.

Most patients will response to this regimen, and it should be maintained for about 12 weeks. One measure at a time may be withdrawn, any recurrence of symptoms indicating its restitution. In this way the minimum maintenance treatment may be determined.

If improvement is inadequate, or can only be maintained at the cost of continuous irksome measures, then surgery should be considered if it is certain that the symptoms are due exclusively to gastro-oesophageal reflux.

REFERENCES

1. Jones RH, Lydeard SE, Hobbs FD *et al.* Dyspepsia in England and Scotland. *Gut* 1990; 31: 401-405.
2. Bennett JR. Chest pain - heart or gullet? *Br Med J* 1983; 286: 1231-1232.
3. Wallin L. Gastro-oesophageal function in duodenal ulcer patients. *Scand J Gastroenterol* 1980; 15: 145-150.
4. Wallin L. Acid gastro-oesophageal reflux pattern in duodenal ulcer patients related to dyspeptic symptoms. *Scand J Gastroenterol* 1980; 15: 151-155.
5. Dent J, Dodds WJ, Freidman RH *et al.* Mechanism of gastro-esophageal reflux in recumbent asymptomatic human subjects. *J Clin Invest* 1980; 65: 256-267.
6. Mittal RK, Large RC, McCallum RW. Identification and mechanism of delayed esophageal acid clearance in subjects with hiatus hernia. *Gastroenternlogy* 1987; 92: 130-135.
7. McCallum RW, Berkowitz DT, Lerner E. Gastric emptying in patients with gastroesophagel reflux. *Gastroenterology* 1981; 80: 285-291.
8. Kaye MD, Showalter JP. Pyloric incompetence in patients with symptomatic gastroesophageal reflux. *J Lab Clin Med* 1974; 83: 198-206.
9. Kruse-Anderson S, Wallin L, Madsen T. Acid gastro-oesophageal reflux and oesophageal pressure activity during post-prandial and nocturnal periods. *Scand J Gastroenterol* 1987; 22: 926-930.
10. Kahrilas PJ, Dodds WJ *et al.* Esophageal peristaltic dysfunction in peptic esophagitis. *Gastroenterology* 1986; 91: 897-904.
11. Helm JF, Dodds WJ, Riedel DR *et al.* Determinants of esophageal acid disease in normal subjects. *Gastroenterology* 1983; 85: 607-612.
12. Collen MJ, Lewis JH, Bengamin SB. Gastric acid hypersecretion in refractory gastro-esophageal reflux disease. *Gastroenterology* 1990; 98: 654-661.
13. Mittal RK, Reuben A, Whiting JO, McCallum RW. Do bile acids reflux into the esophagus? A study in normal subjects and patients with gastroesophageal reflux disease. *Gastroenterology* 1987; 192: 371-375.
14. Orlando RC. Esophageal epithelial resistance. *J Clin Gastroenterol* 1986; 8: 12-16.
15. Bennett JR. pH measurement in the oesophagus. *Bailliere's Clin Gastroenterol* 1987; 1: 747-768.
16. Armstrong D, Monnier PH, Nicolet M, Blum AL, Savarry M. *Gullet* 1991; 1: 63-67.
17. Ismail-Beigi F, Horton PE, Pope CWII. Histological consequence of gastroesophageal reflux in man. *Gastroenterology* 1970; 58: 163-169.
18. Bennett JR, Atkinson M. Oesophageal acid perfusion in the diagnosis of precordial pain. *Lancet* 1966; ii: 1150-1152.
19. Bennett JR. Medical therapy for gastro-oesophageal reflux. In: Hennessy TPJ, Cuschieri A, Bennett JR, eds. *Reflux Oesophagins*. London: Butterworths, 1988.

Annex 9

American Journal of Therapeutics 2, 304–313 (1995)

SELF-DIRECTED TREATMENT OF INTERMITTENT HEARTBURN: A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED EVALUATION OF ANTACID AND LOW DOSES OF AN H_2-RECEPTOR ANTAGONIST (FAMOTIDINE)

Thomas J. Simon,* Roger G. Berlin, Andrea H. Gardner, Laura A. Stauffer, A. Lawrence Gould, and Albert J. Getson

Background: Heartburn, a common symptom, is self-treated with oral antacids. Efficacy of antacids has not been demonstrated for individual, spontaneous heartburn episodes.

Methods: We conducted a double-blind, randomized, placebo-controlled, parallel-group study of self-directed treatment for episodic heartburn comparing famotidine (FAM) 5, 10, or 20 mg and antacid (11 mEq ANC) to placebo (PBO) during a 4-week period. Twenty-nine US investigators enrolled a total of 565 outpatients, ages 18–81 years (mean 44.1 years) with heartburn but not seeking care for heartburn. Treatment of spontaneous heartburn episodes was permitted as needed, up to twice daily, with self-administered test drug. An open-label, backup antacid was provided to use if test drug did not provide adequate relief. Patients assessed heartburn relief hourly and recorded use of backup antacid. Relief was defined as complete relief of symptoms without the use of backup antacid.

Results: The median proportion of episodes relieved was: PBO, 41%; FAM 5 mg, 59%, $0.05 \leq p < 0.10$; FAM 10 mg, 70%, $p < 0.001$; FAM 20 mg, 69%, $p < 0.001$; antacid, 62%, $p < 0.05$ (p-values versus PBO). Supplemental analyses incorporating time to relief confirmed that famotidine and antacid provided more rapid and more frequent relief than placebo (odds ratio for relief relative to PBO: FAM 5 mg, 1.55, $p = 0.003$; FAM 10 mg, 1.94, $p < 0.001$; FAM 20 mg, 2.13, $p < 0.001$; antacid 1.57, $p = 0.003$). The tolerability profile was similar with famotidine, antacid, and placebo.

Conclusions: The positive results with antacid demonstrated for the first time the efficacy of antacid in self-treatment of individual heartburn episodes and provided internal validation of this study paradigm. Patients in this study self-medicated effectively using low doses of famotidine on an as needed basis for spontaneous episodes of heartburn.

Keywords: heartburn, famotidine.

INTRODUCTION

Heartburn and symptoms of indigestion are common; surveys document that approximately 44% of the adult population experiences heartburn at least once a month, and that one in eight experience heartburn two or more times per week [1]. Heartburn episodes have been self-treated using oral antacids, which are believed to work by decreasing acidity within the upper gastrointestinal (GI) tract. However, the efficacy of treatments that decrease intraluminal acidity has not been demonstrated previously for individual, spontaneous heartburn episodes.

Merck Research Laboratories, West Point, USA.
** Address for correspondence: Merck Research Laboratories, P.O. Box 4, West Point, PA 19486, USA.*

This study assessed relief of individual heartburn episodes using treatments that decrease intraluminal acidity by two different methods, neutralizing acid already present in the gut with antacid, and decreasing production of acid, with an antisecretory agent.

The test antacid was a magnesium/aluminum hydroxide preparation, with an acid neutralizing capacity of 11 mEq. This dosage of antacid is widely available and commonly used to treat heartburn.

The test antisecretory agent was an H_2-receptor antagonist, famotidine. Famotidine is a potent, specific, and long-acting agent approved for the treatment of acid-related disorders such as gastric and duodenal ulcer, gastroesophageal reflux disease (GERD), and Zollinger–Ellison syndrome. Its safety and efficacy have been well established in controlled clinical studies.

The purpose of this multicenter, randomized, double-dummy study was to compare the efficacy of antacid and famotidine to placebo in relief of spontaneous, individual heartburn episodes. The study design simulated nonprescription use by employing pocket-size, simple diary cards that provided test medication and self-recorded data on response.

METHODS

Patients

Twenty-nine US centers participated in the study. Institutional review board approval was obtained at each site. Before entry into the study, each patient provided written informed consent after the nature of the study had been fully explained.

Entry required a history of heartburn managed by self-medication with antacid three or more times per week, and the ability to complete a daily diary card accurately. This was confirmed during a 1-week baseline phase; patients had to have at least three episodes of heartburn that improved within 1 h after a single-blind dose of antacid.

Excluded were individuals under 18 years of age, those with significant concurrent disease, hypersensitivity to study medication, or a contraindication to upper GI endoscopy or motility study, and women who were lactating or pregnant. Also excluded were patients who were unable to comply with the protocol, those treated with other investigational drugs within 1 month of entry, or who were expected to require concomitant use of other H_2-receptor antagonists, proton pump inhibitors, prostaglandins, or sucralfate. Concomitant medication was otherwise unrestricted.

Experimental design

This randomized, multicenter, parallel-group trial was conducted in two phases. The baseline phase familiarized subjects with the medication instructions and diary cards. Individuals who did not have heartburn three or more times per week that was at least partially relieved by antacid within 1 h were ineligible for randomization. The 4-week double-blind phase compared the efficacy and safety of five treatments: placebo; famotidine 5 mg, 10 mg, or 20 mg; and antacid. The antacid was chewable recompressed GELUSIL® (magnesium/aluminum hydroxide, ANC = 11.0 mEq). The three famotidine doses were chosen based on previous antisecretory studies demonstrating that 5 mg of famotidine produces an effect on gastric acid secretion similar to 300 mg of cimetidine [2] and that single doses of 5 and 10 mg produced statistically significant decreases in intragastric acidity, beginning at 90–100 min and persisting for approximately 9 h [3].

Treatment was allowed as needed for heartburn, up to twice daily. A pocket-size diary card provided double-dummy test medication and space to record responses to individual doses. The double-dummy design assured the medication blind. At each medication event, patients took both a large tablet (chewed) and a small tablet (swallowed). The large tablet was either antacid or antacid placebo; the small tablet was either famotidine or famotidine placebo. Patients randomized to a famotidine group received an active famotidine tablet and a placebo antacid tablet. Patients randomized to the antacid group received a placebo famotidine tablet and an active antacid tablet. Patients randomized to the placebo group received a placebo famotidine tablet and a placebo antacid tablet. An open-label chewable antacid (WINGEL®, magnesium/aluminum hydroxide; ANC = 12.3 mEq), was provided separately in the event test medication did not provide adequate relief to the patient.

Self-medication instructions (Fig. 1)

When patients developed heartburn requiring self-medication, they recorded the date/time of the episode and the time of last meal and rated the initial severity of the episode. Next, they self-medicated, swallowing a small tablet with water and chewing the large tablet from the diary card. Patients were instructed to observe their symptoms for 1 h without additional treatment.

After 1 h, the episode was considered a success if heartburn was completely relieved ("gone"). If heartburn was not completely relieved after 1 h or anytime subsequently, patients could choose either to use open-label, chewable backup antacid (episode considered a failure) or to continue monitoring. If complete

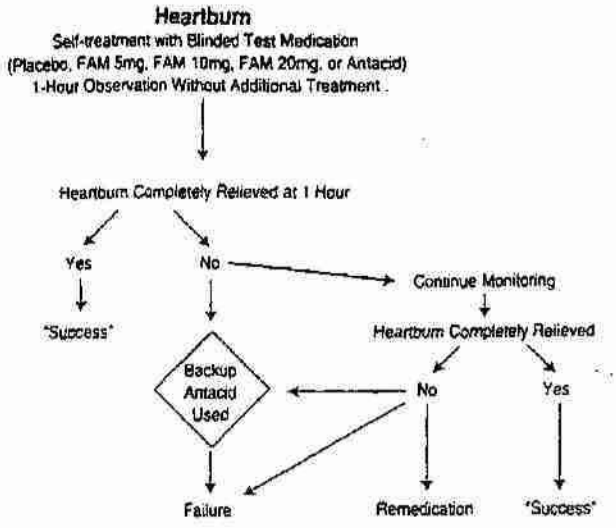


Fig. 1. Daily medication instructions. A total of two doses of test medication permitted per day.

relief occurred without taking backup antacid before the end of the 3-h monitoring period, the episode was considered a success. The episode was considered a failure if complete relief did not occur at all or if backup antacid was taken.

Patients who reached the end of the predefined 3-h monitoring period without complete relief were permitted to take an additional dose of study medication (termed "remedication"). This latter option was used very infrequently (5% of episodes).

Patients completed practice diaries under supervision, and patient diaries were reviewed in detail at each visit. Patients were not instructed to modify their life-style or diet.

Efficacy evaluation

Relief of heartburn episodes

For each dose of medication, patients recorded their response at 1, 2, and 3 h using the following scale: "Compared to when I took test medication, my heartburn is: 1) Completely relieved—Gone; 2) Better—Noticeably improved; 3) Unchanged—Not much different; and 4) Worse—More severe." Open-label antacid (backup) was also noted. The a priori definition of success was: complete relief of heartburn by one or two doses of test medication without use of backup medication.

Relief of the first heartburn episode of the double-blind treatment period was evaluated with additional responses at ½ h and 1½ h after taking the test medication. An episode was defined as ending when a score of "Completely relieved" was recorded.

Global evaluation

At the conclusion of the double-blind phase, patients assessed their response to treatment over the 28-day study period by answering the question, "How did your heartburn respond to test medication?": Excellent, Good, Fair, Poor, None.

Safety evaluation

At each visit, patients reported all adverse experiences since the previous visit. If an individual dropped out early, all procedures scheduled for study conclusion were to be performed.

Safety evaluations also included pretreatment and posttreatment history, physical examination, laboratory evaluations, and upper GI endoscopies (by the same endoscopist, where possible). All patients underwent a pretreatment motility study; a posttreatment study was undertaken only in those cases in which baseline recordings were questionable or abnormal. Because no clinically significant findings were identified, motility results are not discussed in this report.

Statistical planning and analysis

Predefined endpoints and a prioritized ordering of statistical questions were established. The patient was the experimental unit for all analyses. A sample size of 85 subjects per treatment group allowed 80% power to detect a 25% difference in the proportion of episodes relieved between placebo and active treatment (at $\alpha = 0.05$, two-tailed test).

The number of heartburn episodes requiring self-medication was analyzed with a likelihood ratio test based on the Poisson distribution for counts data [4]. The proportion of episodes relieved, the proportion of episodes requiring backup antacid, and the proportion of episodes requiring remedication were calculated for each patient over the double-blind treatment period. The distributions of patient responses were divided into ordered categories to assess proportion of episodes relieved, proportion of episodes requiring backup medication, proportion of episodes requiring remedication, and global evaluation. Groups were compared using a logistic regression model (SAS, PROC LOGISTIC [5]), which included factors for treatment, investigator, and covariates for the severity and number of episodes recorded during the baseline week. Time to relief of first episode was evaluated by survival analysis (Cox regression models) using SAS, PROC PHGLM [6]. A supplemental analysis explicitly incorporated time to relief into the criteria for judging success of all episodes. Each episode was classified into one of four ordered categories: (1) relief within 1 h without backup medication; (2) relief within 2 h

without backup medication; (3) relief within 3 h without backup medication; (4) no relief, or backup medication required. For comparison of treatment groups, each patient provided a set of four numbers, indicating the number of episodes which fell into each category. The proportions of episodes completely relieved within 1, 2, or 3 h were analyzed using a generalized estimating equation version of a method for analyzing ordered categorical outcomes [7] that included the same factors and covariates as the a priori analyses.

The main treatment comparisons of interest were of famotidine versus placebo and antacid versus placebo, although for completeness, all pairwise comparisons were included in the efficacy evaluations.

The reported *p*-values have not been adjusted for multiple comparisons. Multiplicity was addressed by calculation of the O'Brien Global Assessment statistic [8] for the principal endpoints: proportion of episodes relieved, proportion of episodes requiring backup antacid, proportion of episodes requiring remedication, time to relief of first episode, and global evaluation. This calculation was performed after taking into account correlation among endpoints.

Analyses were conducted using an "All-Patients-Treated" approach, which included all patients with both pretreatment and posttreatment data. "Per-Protocol" analyses were also performed, after applying two criteria to identify protocol violators: (1) the patient took concomitant H_2-antagonist therapy, a proton pump inhibitor, sucralfate, or misoprostol, during the double-blind phase of the study ($n = 3$); (2) during the baseline week, the patient had fewer than three episodes of heartburn improved within 1 h by antacid ($n = 62$; one patient met both criteria). All data from the 64 patients who met one or both criteria were excluded from per-protocol analyses.

The per-protocol analyses provide reliable information because most of the exclusions occurred based on information available a priori; data ambiguities were resolved with the investigators; and protocol violators were identified before the blind was broken and the data were analyzed.

RESULTS

Patients

Of 792 patients enrolled in the baseline phase, 227 discontinued before randomization into the double-blind phase (Table 1). The most common reason for discontinuation prior to entry was failure to document that three or more heartburn episodes were at least improved within 1 h of a dose of single-blind antacid

Table 1. Patient accounting.

	n	Percentage [%]
Patients who entered baseline	792	100
Total randomized	565	71
Male (mean age 43.3 years)	306	54
Female (mean age 45.1 years)	259	46
Total discontinued before randomization	227	29
Reasons discontinued		
Clinical adverse experience	5	1
Lost to follow-up	23	3
Protocol deviation	5	1
Patient uncooperative[a]	66	8
Abnormal lab value, baseline	3	0.5
Motility testing not tolerated	8	1
Treatment of new condition	5	1
Inadequate baseline HB/relief	98	12
Improper baseline diary	14	2
Total	227	

[a]Refers to patients who decided not to participate in the study after enrollment, and to patients who did not take test medication for heartburn experienced during the study or did not return to the study site for scheduled visits.

($n = 98$). The mean age of the 565 patients who entered into the double-blind phase was 44.1 years (range: 18–81 years); 54.2% were men (Table 2). Of these 565 patients, 35 were discontinued before completion of the trial, with similar dropout rates in all five treatment groups.

The groups were well matched with regard to demographics, disease characteristics, smoking habits, and alcohol consumption (Table 2). Groups were also well matched with regard to the presence of abnormalities of the upper gastrointestinal mucosa or esophageal motility.

Efficacy

Number of heartburn episodes

The median number of heartburn episodes treated per day was 0.7. Patients treated similar numbers of episodes in all five treatment groups (Table 3). Treatment did not substantially change the tendency to develop heartburn episodes over 4 weeks.

Heartburn relief

Compared to placebo, patients assigned to receive famotidine 5 mg, 10 mg, 20 mg, and antacid reported higher proportions of episodes relieved without use of backup medication; also the patients in the four active treatment groups had smaller proportions of episodes

Table 2. Comparability of treatment groups of randomized patients (n = 565).

		Placebo (n = 111)	Antacid (n = 113)	FAM 5 mg (n = 113)	FAM 10 mg (n = 113)	FAM 20 mg (n = 113)	Total (n = 565)
Age (years)	Mean	43.3	45.3	44.7	43.5	43.7	44.1
	Range	19–73	21–74	20–81	18–77	21–77	18–81
Gender	Female	51 (46.0%)	57 (50.4%)	47 (41.6%)	57 (50.4%)	47 (40.9%)	259 (45.8%)
	Male	60 (54.0%)	56 (49.6%)	66 (58.4%)	56 (49.6%)	68 (59.1%)	306 (54.2%)
Race	Caucasian	97 (87.4%)	100 (88.5%)	101 (89.4%)	103 (91.2%)	102 (88.7%)	503 (89.0%)
	African-American	10 (9.0%)	7 (6.2%)	7 (6.2%)	8 (7.1%)	10 (8.7%)	42 (7.4%)
	Other	4 (3.6%)	6 (5.3%)	5 (4.4%)	2 (1.8%)	3 (2.6%)	20 (3.5%)
Frequency of heartburn	Daily	94 (84.7%)	84 (74.3%)	84 (74.3%)	90 (79.7%)	99 (86.1%)	451 (79.8%)
	Weekly	17 (15.3%)	29 (25.7%)	29 (25.7%)	23 (20.4%)	16 (13.9%)	114 (20.2%)
Most freq. cause of heartburn	Type of food	67 (60.4%)	81 (71.7%)	75 (66.4%)	73 (64.6%)	66 (57.4%)	362 (64.1%)
	Emotional stress	22 (19.8%)	20 (17.7%)	23 (20.4%)	29 (25.7%)	29 (25.2%)	123 (21.8%)
	Overeating	4 (3.6%)	1 (0.9%)	3 (2.7%)	0 (0.0%)	7 (6.1%)	15 (2.7%)
	Other	18 (16.2%)	11 (9.7%)	12 (10.6%)	11 (9.7%)	13 (11.3%)	65 (11.5%)
Smoking	Yes	35 (31.5%)	29 (25.7%)	36 (31.9%)	20 (17.7%)	32 (27.8%)	152 (26.9%)
Alcohol	Yes	12 (10.8%)	10 (8.9%)	15 (13.3%)	14 (12.4%)	13 (11.3%)	64 (11.3%)
Caffeine	Yes	69 (62.2%)	84 (74.3%)	83 (73.5%)	80 (70.8%)	76 (66.1%)	392 (69.4%)
Esophagitis	Grade 0 (None)	48 (43.2%)	45 (39.8%)	40 (35.4%)	50 (44.3%)	49 (42.6%)	232 (41.1%)
	Grade 1	19 (17.1%)	21 (18.6%)	27 (23.9%)	18 (15.9%)	21 (18.3%)	106 (18.8%)
	Grade 2	33 (29.7%)	30 (26.6%)	26 (23.0%)	31 (27.4%)	32 (27.8%)	152 (26.9%)
	Grade 3	9 (8.1%)	13 (11.5%)	14 (12.4%)	10 (8.9%)	12 (10.4%)	58 (10.3%)
	Grade 4	1 (0.9%)	3 (2.7%)	6 (5.3%)	3 (2.7%)	1 (0.9%)	14 (2.5%)
Gastric ulcers	Yes	2 (1.8%)	4 (3.5%)	1 (0.9%)	2 (1.8%)	1 (0.9%)	10 (1.8%)
Duodenal ulcers	Yes	3 (2.7%)	6 (5.3%)	5 (4.4%)	5 (4.4%)	4 (3.5%)	23 (4.1%)
Esophageal motility	Normal	88 (79.3%)	90 (79.7%)	98 (86.7%)	91 (80.5%)	96 (83.5%)	463 (81.9%)
Lower esoph sphincter pressure	Low (<5 mm Hg)	6 (5.4%)	7 (6.2%)	9 (8.0%)	9 (8.0%)	12 (10.4%)	43 (7.6%)

requiring backup antacid. Few episodes for any of the treatment groups required remedication (Table 4). The median time to relief of the first heartburn episode was significantly shorter in the famotidine 5 mg, famotidine 10 mg, and antacid groups than in the placebo group (Table 4). Finally, patients who received famotidine reported more favorable global evaluations than patients who received placebo; using a per-protocol approach, statistically significant advantages favoring famotidine were identified for all three famotidine treatment groups (Fig. 2). In the antacid group, patients reported numerically greater proportions of favorable responses than in the placebo group,

Table 3. Mean number of treated episodes per 14 days, all-patients-treated analysis.

	Treated episodes					
	Weeks 1 and 2		Weeks 3 and 4		Full study	
Treatment group	Rate	SE	Rate	SE	Rate	SE
Placebo	11.84	0.33	11.01	0.32	10.60	0.21
Antacid	11.87	0.32	10.50	0.31	10.70	0.21
FAM 5 mg	11.92	0.33	10.99	0.32	10.55	0.21
FAM 10 mg	11.94	0.33	11.86[a]	0.33	11.10[a]	0.22
FAM 20 mg	11.74	0.32	11.08	0.32	10.83	0.21

Note: Likelihood ratio test based on the Poisson distribution. [a]$0.05 \leq p < 0.10$ versus placebo.

Table 4. Efficacy results, episode-based endpoints.

Treatment	% of episodes relieved (median) (n = 553)	% of episodes requiring backup (median) (n = 553)	% patients w/no episodes requiring remedication (n = 553)	Time to relief of first episode [h] (n = 553)
Placebo	41	43	58	2.0
Antacid	62[a]	32[a]	66	1.5[a]
FAM 5 mg	59[b]	31[a]	65	1.5[a]
FAM 10 mg	70[c]	26[c]	72[a]	1.5[a]
FAM 20 mg	69[c]	26[c]	69[b]	2.0

[a]$p < 0.05$ versus placebo. [b]$0.05 \leq p < 0.10$ versus placebo. [c]$p < 0.001$ versus placebo. Logistic Regression Model. Cox Regression Model (Time to Relief, only).

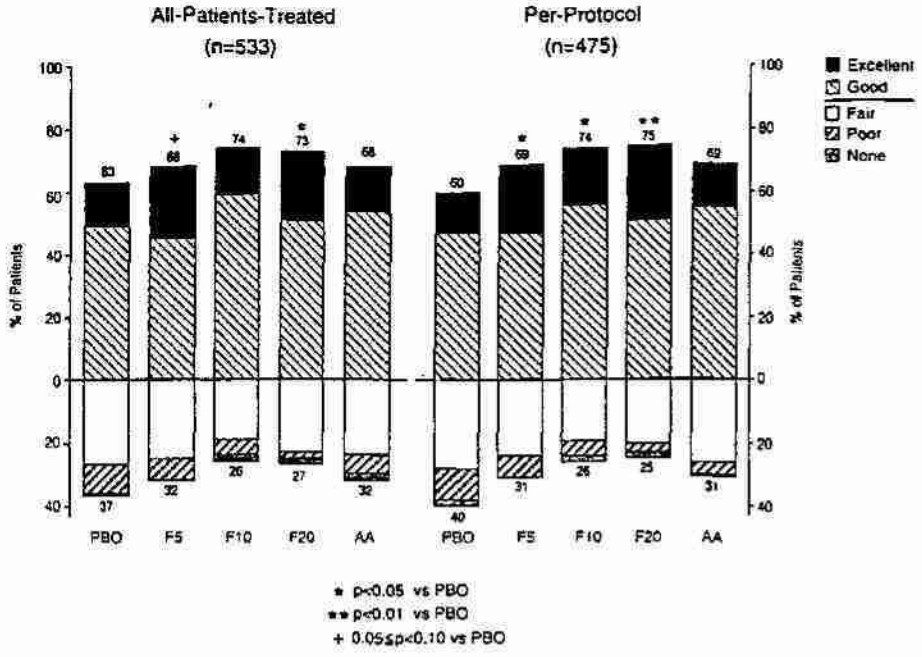


Fig. 2. Percentage of patients assigning each category of global evaluation. The *p*-values are based on the distribution of patients across all five categories. (None, Poor, and Fair are shown below zero; Good and Excellent are shown above zero.)

but formal comparison of the distributions did not demonstrate a statistically significant difference.

To assess whether the pattern of differences versus placebo is a result of multiple statistical tests, an O'Brien global assessment statistic was calculated for each treatment group (Table 5). This statistic takes into account the numerical magnitude of the unadjusted *p*-values and the correlation among endpoints. The O'Brien statistic values indicate that the pattern of differences versus placebo is unlikely to have been observed by chance, supporting the conclusion that the results favoring antacid and famotidine 5 mg, 10 mg, and 20 mg versus placebo are not a statistical artifact due to multiple testing.

Supplemental analysis incorporating time to relief

An additional analysis based on all heartburn episodes was performed to assess relief at 1, 2, and 3 h (Fig. 3), using a definition of success that incorporates the time required to obtain complete relief. This combines all endpoints related to relief of heartburn episodes into a single endpoint. The average percentage of episodes relieved in 1, 2, or 3 h was higher in the famotidine and antacid groups than in the placebo group (Fig. 3). The numerical ordering of the famotidine values at individual time points suggests a dose-response relationship for famotidine 5, 10, and 20 mg.

These data were summarized by calculating an odds ratio for relief relative to placebo. The odds ratio expresses the chance to obtain relief relative to placebo: A value greater than 1.00 indicates that a treatment has a higher chance of providing relief than placebo. The odds ratios (and 95% confidence intervals) show statistically significant advantages versus placebo favoring famotidine 5, 10, and 20 mg and the reference antacid: FAM 5 mg, 1.55 (1.15–2.10), p =

Table 5. O'Brien global assessment statistic and significance values for comparisons versus placebo.

	Treatment Compared to Placebo			
	Antacid	FAM 5 mg	FAM 10 mg	FAM 20 mg
All-patients-treated	2.59 (0.010)	2.92 (0.002)	3.37 (<0.001)	3.27 (<0.001)
Per-protocol	2.86 (0.004)	2.89 (0.002)	3.62 (<0.001)	3.60 (<0.001)

Note: Calculation of O'Brien global assessment statistic [8] for the principal endpoints: proportion of episodes relieved, proportion of episodes requiring backup antacid, proportion of episodes requiring remedication, time to relief of first episode, and global evaluation. Values of this greater than 1.96 correspond to a statistically significant difference versus placebo.

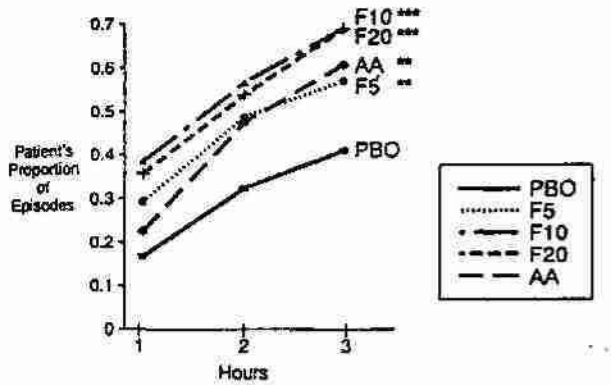


Fig. 3. Median proportion of episodes relieved (per patient) at 1, 2, and 3 h. Note: $^{**}p < 0.01$ vs. placebo; $^{***}p < 0.001$ vs. placebo.

0.003; FAM 10 mg, 1.94 (1.43–2.64), $p < 0.001$; FAM 20 mg, 2.13 (1.55–2.94), $p < 0.001$; antacid 1.57 (1.16–2.11), $p = 0.003$. The numerical ordering of the odds ratios is consistent with a dose-response relationship in the famotidine groups. The reference antacid was also shown more effective than placebo and fell between famotidine 5 mg and famotidine 10 mg.

Relief in patients with and without evidence of esophagitis

Patients underwent endoscopy before double-blind treatment. The presence of esophagitis was assessed endoscopically using a predefined grading scale [9]. To determine how response was affected by the presence of esophageal erosion, heartburn relief was assessed after grouping patients according to the presence or absence of erosive esophagitis (Fig. 4). In patients without evidence of esophagitis, advantages versus placebo were identified favoring all treatments. In patients with evidence of esophagitis, there were advantages versus placebo only in the famotidine 10 and 20 mg treatment groups. These findings indicate that response to antacid and famotidine 5 mg was less pronounced in patients with esophagitis, whereas the response to famotidine 10 and 20 mg was consistent in patients with and without esophagitis.

Clinical/laboratory adverse reactions

The proportion of patients who had an adverse event was similar among treatment groups. Three patients had serious clinical adverse experiences; none was considered related to test drug by the investigator. There were no serious laboratory adverse experiences. Headache was the most common clinical adverse event (Table 6). Six patients who participated in the double-blind phase of the study developed esophagitis that was considered to be an adverse event: Three patients received placebo, one received famotidine 5 mg, one received famotidine 10 mg, and one received famotidine 20 mg. Only one of these adverse events was considered possibly related to test drug, in a patient receiving placebo.

Laboratory adverse events were observed with similar type and frequency in the five treatment groups (data not shown). No laboratory adverse event was considered serious, and no patients were withdrawn for this reason.

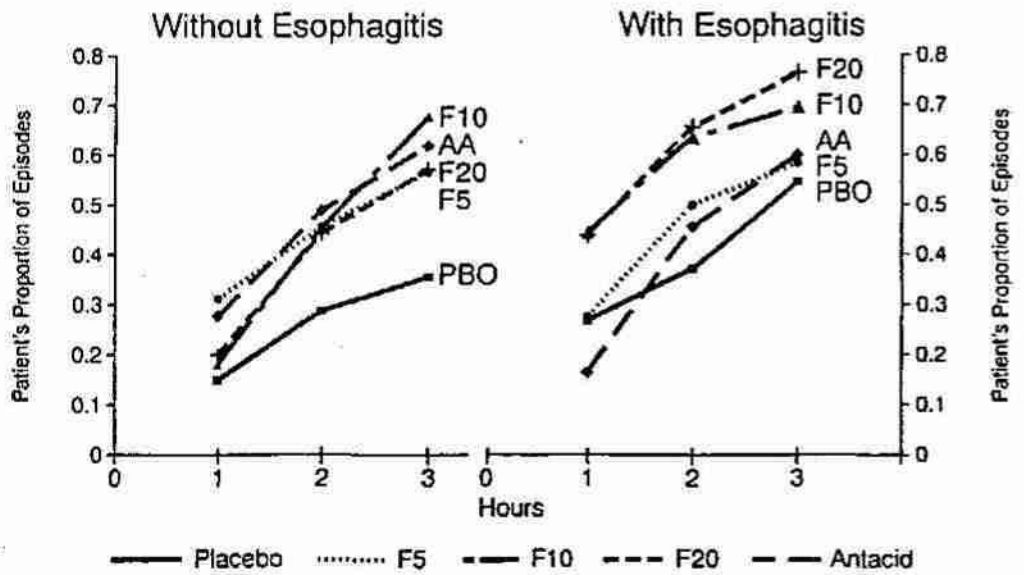


Fig. 4. Median proportion of episodes relieved (per patient) at 1, 2, and 3 h in patients with and without esophagitis at baseline (esophagitis defined as ≥ Grade 2).

Table 6. Most common clinical adverse experiences that began during the double-blind phase (incidence ≥ 5.0% in one or more groups).

	Placebo (n = 111)	Antacid (n = 113)	FAM 5 mg (n = 113)	FAM 10 mg (n = 113)	FAM 20 mg (n = 115)
Diarrhea	3 (3%)	2 (2%)	6 (5%)	6 (5%)	3 (3%)
Headache	10 (9%)	12 (11%)	9 (8%)	11 (10%)	8 (7%)

Endoscopy

A total of 517 patients underwent both pretreatment and posttreatment endoscopy. At baseline, approximately 40% of patients had esophagitis (grade 2, 3, or 4) (Table 2). The distribution of pretreatment and posttreatment esophagitis scores is presented in Table 7: In all treatment groups, most patients had the same endoscopic grade of esophagitis at the baseline and final endoscopies.

No malignancy was detected even though biopsy was required for all gastric ulcers. Two patients developed new gastric or duodenal ulcers during the double-blind phase of the study: One patient who received antacid developed both a gastric and a duodenal ulcer, and one patient who received famotidine 5 mg developed a duodenal ulcer. No bleeding or perforations were observed.

DISCUSSION

This trial was unique in that it allowed medication use as needed, with few constraints on concomitant medication and it facilitated patient data recording by employing a novel diary card that simultaneously presented test medication and space to record outcome of individual medication doses.

In the United States, antacids are considered effective if they neutralize at least 5 mEq acid *in vitro*. Although antacids have been shown to improve symptoms in patients with frequent heartburn and sensitivity to acid [10] and with endoscopically diagnosed reflux esophagitis [11], the efficacy of antacid has not been previously documented with data from spontaneous, individual heartburn episodes.

The results of this study demonstrated that compared to placebo, patients who received antacid documented a higher proportion of episodes relieved without the use of backup medication, a smaller proportion of episodes requiring open-label backup antacid, and a shorter time to relief. These findings show for the first time that antacid is more effective than placebo in relieving individual heartburn episodes.

The data also show that with antacid approximately 50% of heartburn episodes were relieved within 2 h, which is longer than clinical experience suggested. Although partial relief or improvement generally occurred by 1 h (data not shown), episodes that improved without being completely relieved were not considered successfully treated. Therefore, the unexpectedly long time required to obtain relief with antacid reflects the fact that success was defined stringently.

Famotidine was more effective than placebo in this study. Compared to placebo, patients documented a higher proportion of episodes completely relieved without the use of backup medication, a smaller proportion of episodes requiring open-label backup antacid, and a shorter time to relief; there was also a statistically significant advantage versus placebo in patient global assessments. Statistical analyses provide evidence that the profile of efficacy with famotidine and antacid is not a statistical artifact due to multiple comparisons.

The demonstrated effects are clinically relevant. Antacid was associated with a 21 percentage point increase in median proportion of episodes completely relieved. Famotidine treatment (10 mg) was associated with a 29 percentage point increase in the median proportion of episodes completely relieved. Both treatments decreased the proportion of episodes requiring backup medication. The patient global evaluations also provide evidence that the effects are relevant: Both antacid and famotidine were associated with increases in the proportion of patients assigning a good or excellent global evaluation; in the famotidine groups, this difference versus placebo reached statistical significance.

Overall, the efficacy profile of famotidine was generally similar to antacid: Approximately 50% of episodes were completely relieved within 2 h with both antacid and famotidine. The most likely explanation for this longer than expected time interval (particularly for antacid) is that complete disappearance of symptoms was required for an episode to be considered relieved; an episode in which symptoms decreased partially was not considered relieved in this study.

Table 7. Distribution of patients according to baseline and final esophagitis grade.

Baseline Esophagitis Grade	Final Esophagitis Grade: 0	1	2	3	4	Total
0	All Groups 181 (68.6)	All Groups 15 (15.5)	All Groups 14 (13.5)	All Groups 0	All Groups 0	Total Grade 0 at Baseline 210
	P 35 (13.3)	P 5 (5.2)	P 4 (3.8)	P 0	P 0	P 44
	AA 37 (14.0)	AA 2 (2.1)	AA 0	AA 0	AA 0	AA 39
	F5 30 (11.4)	F5 3 (3.1)	F5 4 (3.8)	F5 0	F5 0	F5 37
	F10 40 (15.2)	F10 3 (3.1)	F10 2 (1.9)	F10 0	F10 0	F10 45
	F20 39 (14.8)	F20 2 (2.1)	F20 4 (3.8)	F20 0	F20 0	F20 45
1	All Groups 40 (15.2)	All Groups 47 (48.5)	All Groups 6 (5.8)	All Groups 2 (4.5)	All Groups 1 (12.5)	Total Grade 1 at Baseline 96
	P 8 (3.0)	P 6 (6.2)	P 1 (1.0)	P 1 (2.3)	P 0	P 16
	AA 8 (3.0)	AA 10 (10.3)	AA 1 (1.0)	AA 0	AA 1 (12.5)	AA 20
	F5 7 (2.7)	F5 15 (15.5)	F5 1 (1.0)	F5 0	F5 0	F5 23
	F10 10 (3.8)	F10 5 (5.2)	F10 2 (1.9)	F10 0	F10 0	F10 17
	F20 7 (2.7)	F20 11 (11.3)	F20 1 (1.0)	F20 1 (2.3)	F20 0	F20 20
2	All Groups 41 (15.5)	All Groups 28 (28.9)	All Groups 67 (64.4)	All Groups 4 (9.1)	All Groups 1 (12.5)	Total Grade 2 at Baseline 141
	P 7 (2.7)	P 4 (4.1)	P 16 (15.4)	P 3 (6.8)	P 1 (12.5)	P 31
	AA 7 (2.7)	AA 8 (8.2)	AA 10 (9.6)	AA 0	AA 0	AA 25
	F5 7 (2.7)	F5 4 (4.1)	F5 13 (12.5)	F5 0	F5 0	F5 24
	F10 10 (3.8)	F10 5 (5.2)	F10 14 (13.5)	F10 0	F10 0	F10 29
	F20 10 (3.8)	F20 7 (7.2)	F20 14 (13.5)	F20 1 (2.3)	F20 0	F20 32
3	All Groups 1 (0.4)	All Groups 7 (7.2)	All Groups 16 (15.4)	All Groups 31 (70.5)	All Groups 1 (12.5)	Total Grade 3 at Baseline 56
	P 0	P 0	P 3 (2.9)	P 8 (13.6)	P 0	P 9
	AA 0	AA 0	AA 2 (1.9)	AA 11 (25.0)	AA 0	AA 13
	F5 1 (0.4)	F5 1 (1.0)	F5 5 (4.8)	F5 5 (11.4)	F5 1 (12.5)	F5 13
	F10 0	F10 2 (2.1)	F10 3 (2.9)	F10 5 (11.4)	F10 0	F10 10
	F20 0	F20 4 (4.1)	F20 3 (2.9)	F20 4 (9.1)	F20 0	F20 11
4	All Groups 1 (0.4)	All Groups 0	All Groups 1 (1.0)	All Groups 7 (15.9)	All Groups 5 (62.5)	Total Grade 4 at Baseline 14
	P 1 (0.4)	P 0	P 0	P 0	P 0	P 1
	AA 0	AA 0	AA 0	AA 1 (2.3)	AA 2 (25.0)	AA 3
	F5 0	F5 0	F5 1 (1.0)	F5 2 (4.5)	F5 3 (37.5)	F5 6
	F10 0	F10 0	F10 0	F10 3 (6.8)	F10 0	F10 3
	F20 0	F20 0	F20 0	F20 1 (2.3)	F20 0	F20 1
Total	Total Grade 0 at Final 264	Total Grade 1 at Final 97	Total Grade 2 at Final 104	Total Grade 3 at Final 44	Total Grade 4 at Final 8	Total w/ Baseline and Final 517
	P 51 (19.3)	P 15 (15.5)	P 24 (23.1)	P 10 (22.7)	P 1 (12.5)	P 101
	AA 52 (19.7)	AA 20 (20.6)	AA 13 (12.5)	AA 12 (27.3)	AA 3 (37.5)	AA 100
	F5 45 (17.0)	F5 23 (23.7)	F5 24 (23.1)	F5 7 (15.9)	F5 4 (50.0)	F5 103
	F10 60 (22.7)	F10 15 (15.5)	F10 21 (20.2)	F10 8 (18.2)	F10 0	F10 104
	F20 56 (21.2)	F20 24 (24.7)	F20 22 (21.2)	F20 7 (15.9)	F20 0	F20 109

Note: Percent (indicated in parentheses) is calculated using the total number of patients for each final esophagitis grade appearing in bold print. *Predefined esophagitis grading scale* [9] was used.

Supplemental analyses which took time into account demonstrated that famotidine substantially accelerated the time to relief compared to placebo and that the effects of famotidine 5 mg are similar to antacid. This type of analysis also demonstrated a difference between famotidine and antacid in this study: Famotidine 10 mg and 20 mg were effective versus placebo in patients with and without erosive esophagitis at baseline, whereas antacid and famotidine 5 mg offered a clear advantage versus placebo only in patients without evidence of esophagitis at baseline.

Although the study was not specifically designed to distinguish among famotidine doses, there was numerical evidence of a dose-response relationship in proportion of episodes relieved at 1, 2, and 3 h. These findings suggest that famotidine 10 mg is an optimal dose: Famotidine 10 and 20 mg appeared more effective than famotidine 5 mg; however, famotidine 20 mg did not provide meaningful additional benefit.

For over-the-counter (OTC) use, safety is of paramount concern. In this trial, the safety profile of famotidine was comparable to that of placebo and antacid and was consistent with the previously estab-

lished excellent safety profile of famotidine. Results of pretreatment and posttreatment endoscopic examinations provide evidence that self-treatment of upper GI symptoms with famotidine or antacid does not lead to deterioration in potential underlying conditions of the upper gastrointestinal mucosa. Although a significant proportion of patients (approximately 40%) were found to have esophagitis grade 2 or greater (erosive esophagitis), over the 4-week double-blind period, the proportion of patients with esophagitis decreased numerically, and no complications of acid peptic disease (hemorrhage, perforation, or stricture) were observed. In addition, self-treatment of upper GI symptoms is unlikely to cause a substantial delay in seeking diagnostic evaluation; neither famotidine nor antacid treatment significantly reduced the number of heartburn episodes.

Data from this trial document for the first time the superiority of antacid to placebo in individual spontaneous heartburn episodes. Our results demonstrated that for intermittent heartburn, famotidine 10 mg was superior to placebo and well tolerated by patients as a self-medication in this study. Raising intraluminal acidity with antacid or a low dose of H_2-receptor antagonist was effective in treating intermittent heartburn in this study.

INVESTIGATORS

Primary Investigator(s)/Location
Mark Blitstein, MD, Lake Bluff, IL
Warwick Charlton, MD/Paula Barden, MD, Albuquerque, NM
Gregory V. Collins, MD, Charlotte, NC
Harry Collins, MD, Edison, NJ
Robert J. Dockhorn, MD, Prairie Village, KS
Ernest Dorsch, MD, Houston, TX
Roy Fleischmann, MD, Dallas, TX
Robert L. Frachtman, MD, Austin, TX
Joseph Geenen, MD, Racine, WI
David Ginsberg, DO, Harleysville, PA
Norman Gitlin, MD, Fresno, CA
Daniel Gremillion, MD, Nashville, TN
Peter Karras, MD/David Steward, MD, Springfield, IL
Frank Lanza, MD, Houston, TX
F. Martin Lester, MD, Mobile, AL
David J. Miller, DO, Morrisville, PA
Daniel Pertchuk, MD, Encinitas, CA
Stanley J. Pietrak, MD, Buffalo, NY
David Pitts, MD/Jane Pitts, MD, Chattanooga, TN
William G. Rector, Jr., MD, Denver, CO
Malcolm G. Robinson, MD, Oklahoma City, OK
Seymour M. Sabesin, MD, Chicago, IL
Paul K. Schlesinger, MD, Chicago, IL
Harry Serfer, DO, Hollywood, FL
John Stancher, MD, Madison, WI
Philip D. Toth, MD, Indianapolis, IN
Z. Reno Vlahcevic, MD, Richmond, VA
Eric Martin Wall, MD, Portland, OR
Alvin Zfass, MD, Richmond, VA

REFERENCES

1. The Gallup Organization: *The Gallup Organization: Gallup Survey on Heartburn Across America*, The Gallup Organization, 1988.
2. McCallum RW, Chremos AN, Kuljian B, Tupy-Visich MA, Huber PB: MK-208, A novel histamine H_2-receptor inhibitor with prolonged antisecretory effect. Dig Dis Sci 1985;30:1139–1144.
3. Laskin OL, Patterson PM, Shingo S, Lasseter KC, Shamblen EC: Pharmacodynamics and dose-response relationship of famotidine: a double-blind randomized placebo-controlled trial. J Clin Pharmacol 1993;33:636–639.
4. McCullagh P, Nelder JA: Likelihood functions. *Generalized Linear Models*, Chapman & Hall, London, 1989, pp. 194–200.
5. McCullagh P: Regression models for ordinal data. J Roy Statist Soc 1980;42(Series B):102–142.
6. Cox DR: Regression models and life tables. J Roy Statist Soc 1972;34(Series B):187–220.
7. McCullagh P, Nelder JA: Quasi-likelihood functions, *Generalized Linear Models*, Chapman & Hall, London, 1989, pp. 323–352.
8. O'Brien PC: Procedures for comparing samples with multiple endpoints. Biometrics 1984;40:1079–1087.
9. Hetzel DJ, Dent J, Reed WD et al: Healing and relapse of severe peptic esophagitis after treatment with omeprazole. Gastroenterology 1988;95:903–912.
10. Graham DY, Patterson DJ: Double-blind comparison of liquid antacid and placebo in the treatment of symptomatic reflux esophagitis. Dig Dis Sci 1983;28:559–563.
11. Farup PG, Weberg R, Berstad A, Wetterhus S, Dahlberg O, Dybdahl G, Fyllingen G, Kannelonning KS, Lange O: Low-dose antacids versus 400 mg cimetidine twice daily for reflux oesophagitis: a comparative, placebo-controlled, multicentre study. Scand J Gastroenterol 1990;25:315–320.

Annex 10

COMMITTEE	:	**DRAFT ADVICE**
DATE OF MEETING	:	**March 2000**
M.A. No	:	**PL 00025/0312 and 0313**
COMPANY	:	**Merck Sharp and Dohme Ltd**
PRODUCT	:	**Pepcid AC Tablets & Pepcid AC**
	:	**Chewable Tablets**
ACTIVE CONSTITUENT	:	**Famotidine**
LEGAL STATUS	:	**P to GSL**
KEY WORDS		

APPLICATION FOR A NATIONAL VARIATION TO A MARKETING AUTHORISATION FOR ADDITIONAL STATUS AS A GSL PRODUCT FOR PEPCID AC TABLETS AND PEPCID AC CHEWABLE TABLETS

LEGAL CLASSIFICATION

The Committee considered whether Pepcid AC Tablets and Pepcid AC Chewable Tablets fall within a description or class specified for the purpose of Section 51 of the Medicines Act 1968 by Order made under Section 51 (1), as being appropriate for supply with reasonable safety, otherwise than by, or under the supervision of, a pharmacist and advised that the GSL Order be amended to allow general sale supply.

The Committee also advised that:-

i. An entry should be made for famotidine in the Medicines (Products Other than Veterinary Drugs) (General Sales List Order) 1984 to allow general sale up to a maximum dose of 10mg and a maximum daily dose up to 20mg.

ii. An entry should be made for famotidine in the medicines (Sale and Supply) (Miscellaneous Provisions) Regulations 1980 to allow up to 12 x 10mg tablets of famotidine to be sold otherwise than at a registered pharmacy.

PRODUCT INFORMATION

The Committee advised that the variation should be granted on condition that the product particulars are amended and in particular:-

1. Summary of Product Characteristics

1.1 Name of Medicinal Product

An alternative product name should be proposed.

1.2 Posology and Method of Administration

The maximum treatment duration is amended to read "Do not take for more than 6 days or purchase a second pack of tablets without the advice of a pharmacist or doctor".

1.3 Special Warnings and Precautions

The following should be added:

i) Treatment with a histamine H_2-receptor antagonist may mask symptoms associated with carcinoma of the stomach, and may therefore delay diagnosis of the condition.

ii) Patients who are taking non-steroidal anti-inflammatory drugs, especially the elderly, should consult their doctor before taking this product.

2. Patient Information Leaflet/Labelling

The patient information leaflets and the labelling should be amended to be consistent with the SPC and to the satisfaction of the Secretariat. Reference to the contra-indications and special warnings and precautions should be included on the outer carton. Promotional statements should be removed from the carton. Suitable information on life-style changes to improve the symptoms should be included in the leaflet.

COMMERCIAL IN CONFIDENCE	**NUMBER:** PL 0025/0312
APPLICATION FOR A PRODUCT LICENCE:	**PRODUCT NAME:** Blocazide 10mg Film-coated Tablets
PROPOSED LICENCE HOLDER: Merck Sharp and Dohme Ltd Hertford Road Hoddesdon Herts EN11 9BU	**THERAPEUTIC CLASSIFICATION:** H_2-receptor antagonist **RECEIVED:** 27 January 1993 **MEETING:** May 1993
MANUFACTURER OF DOSAGE FORM: Woelm Pharma GMBH, Eschwege, Germany or MSD, Cramlington, Northumberland, UK or MSD (Italia), Pavia, Italy **LEGAL STATUS:** P	**COMMITTEE ON SAFETY OF MEDICINES** **SAFETY AND EFFICACY SUB-COMMITTEE** **CONSIDERATION BY OTHER COMMITTEES:** **Chemistry Pharmacy and Standards** **Sub-Committe on Pharmacovigilance**
SALE/SUPPLY: Through registered pharmacies, under the supervision of a Pharmacist	**ASSESSED BY:** [redacted]

SUMMARY

An abridged application for a lower strength famotidine film coated tablet (10mg) available for use as short-term treatment on an "as required" basis for "the treatment of indigestion, acid indigestion, nervous indigestion, heartburn, dyspepsia, acidity and symptoms of upset stomach associated with these conditions".

Efficacy for the short-term symptomatic relief of heartburn, dyspepsia and hyperacidity demonstrated.

Adequate evidence of safety submitted.

Famotidine 10mg to be used as needed to relieve symptoms or 1 hour prior to eating food and/or beverages known to provoke symptoms.

No bar to the grant of Pharmacy status for this 10mg formulation of famotidine.

INDEX

A 1

Form MLA 201

PRODUCT PARTICULARS - a complete set of pages should be included for each strength of product

PL Number of Product: (Official use only)

1. Name of Product and Strength: *BLOCAZIDE 10 MG*

(Official use only)

2. Full description of Pharmaceutical form (eg tablets, slow-release tablets, capsules etc):

FILM-COATED TABLET FOR ORAL ADMINISTRATION TO HUMAN BEINGS.

(Official use only)

(Official use only)

3a. Legal status requested (please tick in appropriate box)

(Official use only)

Prescription		Pharmacy	X	General Sales		Not Applicable	

3b. Method of retail sale or supply: *FOR SUPPLY TO MEMBERS OF THE GENERAL PUBLIC THROUGH REGISTERED PHARMACIES, UNDER THE SUPERVISION OF A PHARMACIST.*

(Official use only)

Text should be completed in block capitals

Date: *24 JANUARY 1993*

(Official Use Only)

D	1						/											

4. Active Constituents

(Official use only)	Name	Specification Reference			Quantity/Dose Unit or % quantity					Unit	
	FAMOTIDINE	*U*	*S*	*P*		*1*	*0 • 0*			*M*	*G*
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				

Details of any overages:- these should not be included in the Formulation Columns but stated in this section.

1) Please enter constituent(s) as actual substances included in the formulation, eg. as salt and then as base equivalent where applicable.

2) See page E1, paragraph 2 for approved abbreviations

Where a Specification does not refer to the latest published monograph, the relevant year should be included in the Name Column and set in the Specification Reference Column. Where an ingredient has no official monograph please enter HSE in the Specification Reference Column.

3) In the case of liquid preparations: all quantities for oral preparations should relate to a 5 ml dosage. Please state in dosage information any deviation from this rule. Quantity should be expressed as a percentage for other liquid preparations, including parenterals please insert WW, WV etc as appropriate in the Unit Column. DO NOT INSERT a percentage sign, this is automatically inserted by computer.

4) The following abbreviations for units are recommended:-
NG nanogrammes; UG microgrammes; MG milligrammes; GM grammes; KG kilogrammes; UL microlitres; ML millilitres; L litres; U units (u); KU kilounits (1,000 u); MU megaunits (1,000,000 u); I.U. international units; UC microcuries; BC becquerels.

5) Trailing zeros following the decimal point may be omitted eg. 10.02 mg will suffice.

6) Please photocopy page if more space for constituents is required.

Date: *24 JANUARY 1993*

C	1						/											

5. Recommended clinical indications and route(s) of administration

TREATMENT OF:

- *INDIGESTION*
- *ACID INDIGESTION*
- *NERVOUS INDIGESTION*
- *HEARTBURN*
- *DYSPEPSIA*
- *ACIDITY*
- *SYMPTOMS OF UPSET STOMACH ASSOCIATED WITH THESE CONDITIONS*

ROUTE OF ADMINISTRATION: ORAL

(Official use only)

All entries must be made in full. Cross references, eg. to accompanying data sheets are not acceptable.

Date: *24 JANUARY 1993*

B 1 / /

6. Recommended doses and dosage schedules:

Distinguish between adults, children and the elderly and between different clinical indications

(Official Use Only)

ADULTS AND CHILDREN 12 YEARS OF AGE OR OLDER:
DOSAGE: 10 MG.

DOSAGE INTERVAL: AS NEEDED TO RELIEVE SYMPTOMS OR ONE HOUR BEFORE EATING FOR SYMPTOMS ASSOCIATED WITH FOOD AND BEVERAGE.

MAXIMUM INTAKE IN 24 HOURS: 20 MG.

NO DOSAGE ADJUSTMENT IS NECESSARY FOR THE ELDERLY.

(Official use only)

Date: *24 JANUARY 1993*

B	2						/										

7. Contraindications, Precautions and Warnings listed, with titles. In the following order:-

a) Contraindications
b) Interactions with other medicaments and other forms of interaction
c) Effects on ability to drive and to use machines
d) Other undesirable effects (frequency and seriousness)
e) Use in pregnancy and lactation
f) Other special warnings and precautions
g) Overdose (symptoms, emergency procedures, antidotes)
h) Incompatibilities (major)

A) CONTRAINDICATIONS

HYPERSENSITIVITY TO ANY COMPONENT OF THIS PRODUCT.

B) INTERACTIONS WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION

NO DRUG INTERACTIONS OF CLINICAL IMPORTANCE HAVE BEEN IDENTIFIED. 'BLOCAZIDE' DOES NOT INTERACT WITH THE CYTOCHROME P450-LINKED DRUG METABOLIZING ENZYME SYSTEM. COMPOUNDS METABOLIZED BY THIS SYSTEM WHICH HAVE BEEN TESTED IN MAN HAVE INCLUDED WARFARIN, THEOPHYLLINE, PHENYTOIN, DIAZEPAM, PROPRANOLOL, AMINOPYRINE AND ANTIPYRINE. INDOCYANINE GREEN AS AN INDEX OF HEPATIC BLOOD FLOW AND/OR HEPATIC DRUG EXTRACTION HAS BEEN TESTED AND NO SIGNIFICANT EFFECTS HAVE BEEN FOUND.

CONCOMITANT USE OF ALUMINIUM HYDROXIDE/MAGNESIUM HYDROXIDE DOES NOT INFLUENCE THE PHARMACODYNAMICS OR BIOAVAILABILITY OF 'BLOCAZIDE'.

'BLOCAZIDE' DOES NOT AFFECT BLOOD ALCOHOL LEVELS FOLLOWING ORAL INGESTION OF ETHANOL.

C) EFFECTS ON ABILITY TO DRIVE AND OPERATE MACHINERY

NONE KNOWN.

D) OTHER UNDESIRABLE EFFECTS (FREQUENCY AND SERIOUSNESS)

'BLOCAZIDE' HAS BEEN DEMONSTRATED TO BE GENERALLY WELL-TOLERATED. SIDE EFFECTS REPORTED IN $\geq$1% OF PATIENTS WERE HEADACHE AND DIZZINESS. THESE OCCURRED WITH COMPARABLE FREQUENCY IN PATIENTS TREATED WITH PLACEBO.

E) USE IN PREGNANCY AND LACTATION

CLINICAL TRIALS IN PREGNANT WOMEN HAVE NOT BEEN PERFORMED. AS WITH MOST MEDICINES, 'BLOCAZIDE' IS NOT RECOMMENDED FOR USE IN PREGNANCY, AND SHOULD BE USED ONLY UNDER THE ADVICE OF A PHYSICIAN.

FAMOTIDINE IS DETECTABLE IN HUMAN MILK. NURSING MOTHERS SHOULD NOT TAKE THIS DRUG OR SHOULD STOP NURSING.

(Official use only)

Date: *24 JANUARY 1993*

B	2						/										

7. Contraindications, Precautions and Warnings listed, with titles. In the following order:-

a) Contraindications
b) Interactions with other medicaments and other forms of interaction
c) Effects on ability to drive and to use machines
d) Other undesirable effects (frequency and seriousness)
e) Use in pregnancy and lactation
f) Other special warnings and precautions
g) Overdose (symptoms, emergency procedures, antidotes)
h) Incompatibilities (major)

E) *USE IN PREGNANCY AND LACTATION (CONTINUED)*

REPRODUCTIVE STUDIES HAVE BEEN PERFORMED IN RATS AND RABBITS AT ORAL DOSES OF UP TO 2000 AND 500 MG/KG/DAY, RESPECTIVELY (APPROXIMATELY 5000 AND 1250 TIMES THE MAXIMUM RECOMMENDED HUMAN DOSE, RESPECTIVELY), AND HAVE REVEALED NO EVIDENCE OF IMPAIRED FERTILITY OR HARM TO THE FETUS DUE TO FAMOTIDINE.

IN STUDIES WITH RATS GIVEN ORAL DOSES OF UP TO 2000 MG/KG/DAY OR INTRAVENOUS DOSES OF 200 MG/KG/DAY (APPROXIMATELY 5000 AND 500 TIMES THE MAXIMUM RECOMMENDED HUMAN DOSE, RESPECTIVELY), FERTILITY AND REPRODUCTIVE PERFORMANCE WERE NOT AFFECTED.

F) *OTHER SPECIAL WARNINGS AND PRECAUTIONS*

IN CLINICAL TRIALS, PATIENTS WITH OTHER UNDERLYING ACID GASTROINTESTINAL DISEASES (EG, DUODENAL ULCER, GASTRIC ULCER) DID NOT EXPERIENCE COMPLICATIONS; IN GENERAL, THEY DID NOT EXHIBIT A CLINICALLY SIGNIFICANT DETERIORATION IN THEIR CONDITION. HOWEVER, IF PATIENTS HAVE DIFFICULTY SWALLOWING OR ABDOMINAL DISCOMFORT PERSISTS THE UNDERLYING CAUSE SHOULD BE DETERMINED.

THERAPY SHOULD NOT EXCEED TWO WEEKS WITHOUT MEDICAL CONSULTATION.

WHEN 'BLOCAZIDE' WAS ADMINISTERED TO ELDERLY PATIENTS IN CLINICAL TRIALS, NO INCREASE IN THE INCIDENCE OR CHANGE IN THE TYPE OF DRUG-RELATED SIDE EFFECTS WAS OBSERVED.

G) *OVERDOSE*

PATIENTS HAVE TOLERATED DOSES UP TO 800 MG/DAY FOR MORE THAN A YEAR WITHOUT DEVELOPMENT OF SIGNIFICANT SIDE EFFECTS.

H) *INCOMPATIBILITIES*

NONE.

(Official use only)

Date: *24 JANUARY 1993*

E	1						/										

8. Other Constituents

(Official use only)	Name	Specification Reference			mod	Quantity/Dose Unit or % quantity		Unit	
	TABLET CORE:								
	MAGNESIUM STEARATE	*E*	*P*					*M*	*G*
	MICROCRYSTALLINE CELLULOSE	*E*	*P*					*M*	*G*
	PREGELATINISED MAIZE STARCH	*B*	*P*					*M*	*G*
	TALC	*E*	*P*					*M*	*G*
	INDUSTRIAL METHYLATED SPIRIT (OR ALCOHOL 95%	*B* *U*	*P* *S*	*P)*					
	PURIFIED WATER	*E*	*P*						
	TABLET COAT:								
	HYDROXYPROPYL-CELLULOSE	*E*	*P*					*M*	*G*
	METHYLHYDROXY-PROPYLCELLULOSE	*E*	*P*					*M*	*G*
	RED IRON OXIDE E172	*E*	*E*	*C*			*2*	*M*	*G*
	TALC	*E*	*P*					*M*	*G*
	TITANIUM DIOXIDE E171	*E*	*P*					*M*	*G*
	PURIFIED WATER	*E*	*P*						

1) Please leave a line between different components of the dosage form, eg. for capsule shell components, coating components.
2) Where a specification reference does not refer to the latest published monograph, the relevant year should be included in the Name Column and not in the Specification Reference Column. Where an ingredient has no official monograph please enter HSE in the Specification Reference Column. Abbreviations to be used for specification are:- BP, EP, BPC, BNF, USP, NF, FRP, DAB, IP, NDP, JAP, PHV, BHP.
3) Please complete modifier column marked MOD as follows:
   Insert TO if final volume cannot be expressed as a complete quantity.
   Insert ND for substances not detectable in the final formulation, eg. solvents.
   Insert QS if quantity not fixed eg. for substances used to adjust pH.
4) Recommended abbreviations for units are given on page D1, paragraph 4.
5) In the case of liquid preparations: all quantities for oral preparations should relate to a 5 ml dosage. Please state in dosage information any deviation from this rule. Quantity should be expressed as a percentage for other liquid preparations, including-parenterals please insert WW, WV etc as appropriate in the Unit Column. DO NOT INSERT a percentage sign, this is automatically inserted by computer.
6) Trailing zero's following the decimal point may be omitted eg. 10.02 mg will suffice.
7) Please photocopy page if more space for constituents is required.

Date: *24 JANUARY 1993*

H	1						/										

9. Description of essential processes in the manufacture:

FAMOTIDINE, MICROCRYSTALLINE CELLULOSE, AND PREGELATINISED MAIZE STARCH ARE GRANULATED WITH A WATER/ETHANOL MIXTURE, DRIED, MILLED, LUBRICATED WITH MAGNESIUM STEARATE AND TALC, AND COMPRESSED INTO TABLETS.

THE TABLET COATING SUSPENSION IS PREPARED BY DISPERSING THE METHYLHYDROXYPROPYL-CELLULOSE AND HYDROXYPROPYLCELLULOSE IN THE PURIFIED WATER AND THEN DISPERSING THE TITANIUM DIOXIDE, TALC AND RED IRON OXIDE IN THIS SOLUTION. THE SUSPENSION IS SPRAYED ON THE COMPRESSED TABLETS IN A STANDARD COATING PAN.

10. Finished Product Specification:

APPEARANCE:	*PALE-ROSE (PINK), ROUNDED-SQUARE, FILM-COATED TABLET WITH THE TRADEMARK PRINTED ON ONE SIDE.*
IDENTITY:	*CONFIRMED BY HPLC (OR ALTERNATIVE TLC METHOD).*
FAMOTIDINE ASSAY:	[redacted]
DEGRADATES:	[redacted]
UNIFORMITY OF CONTENT:	*MEETS THE EP/USP SPECIFICATION.*
DISSOLUTION:	[redacted]

Date: *24 JANUARY 1993*

G	1					/										

11. Arrangements for storage and address(es) of storage premises:

BULK TABLETS WILL BE STORED BRIEFLY AT THE SITE OF MANUFACTURE AND THE SITE OF ASSEMBLY. FINISHED PRODUCT WILL BE STORED BRIEFLY AT THE SITE OF ASSEMBLY, AND FOR DISTRIBUTION AT MSD, CRAMLINGTON, UK.

12. Special precautions for storage:

STORE BELOW 30°C; PROTECT FROM MOISTURE.

13. Nature of container and closure | Shelf-life (A) | Shelf-life (B) | Pack Size

Nature of container and closure	Shelf-life (A)	Shelf-life (B)	Pack Size
OPAQUE HDPE BOTTLES WITH LDPE CLOSURES.	*2 4 M*		*3 0*
			4 0
			5 0

Unit

Notes: 1) Shelf-life should be expressed in months (M), weeks (W) or days (D) as appropriate eg 3 6 M
A = Unopened.
B = After reconstitution or when the container is opened for the first time, if appropriate.

2) The pack size should contain numbers only, right aligned. If a decimal point is required it should occupy one box.

3) Where applicable enter the unit of measure as MG, GM, ML, LT in the Unit box. No entry is required in the Unit box for solid dosage forms.

Date: *24 JANUARY 1993*

G	1						/										

11. Arrangements for storage and address(es) of storage premises:

BULK TABLETS WILL BE STORED BRIEFLY AT THE SITE OF MANUFACTURE AND THE SITE OF ASSEMBLY. FINISHED PRODUCT WILL BE STORED BRIEFLY AT THE SITE OF ASSEMBLY, AND FOR DISTRIBUTION AT MSD, CRAMLINGTON, UK.

12. Special precautions for storage:

STORE BELOW 30°C; PROTECT FROM MOISTURE.

13. Nature of container and closure | Shelf-life (A) | Shelf-life (B) | Pack Size

Nature of container and closure	Shelf-life (A)	Shelf-life (B)	Pack Size
BLISTER PACKS WITH PVC BASE AND ALUMINIUM FOIL LIDDING.	*24M*		*2*
			6
			10
			12
			18
			20

Unit

Notes: 1) Shelf-life should be expressed in months (M), weeks (W) or days (D) as appropriate eg 3 6 M
A = Unopened.
B = After reconstitution or when the container is opened for the first time, if appropriate.

2) The pack size should contain numbers only, right aligned. If a decimal point is required it should occupy one box.

3) Where applicable enter the unit of measure as MG, GM, ML, LT in the Unit box. No entry is required in the Unit box for solid dosage forms.

Date: *24 JANUARY 1993*

K 1 / [ ]

14. Pharmacological particulars:

'BLOCAZIDE' IS A POTENT COMPETITIVE H_2-RECEPTOR ANTAGONIST.

'BLOCAZIDE' HAS A RAPID ONSET OF ACTION FOLLOWING ORAL ADMINISTRATION AND, AT THE RECOMMENDED DOSES, 'BLOCAZIDE' HAS A LONG DURATION OF ACTION AND IS HIGHLY EFFECTIVE AT RELATIVELY LOW BLOOD CONCENTRATIONS. DURATION OF ACTION, PLASMA CONCENTRATION, AND URINARY RECOVERY ARE DOSE-RELATED.

'BLOCAZIDE' REDUCES THE ACID AND PEPSIN CONTENT, AS WELL AS THE VOLUME, OF BASAL, NOCTURNAL, AND STIMULATED GASTRIC SECRETION.

IN CLINICAL TRIALS 'BLOCAZIDE' PROVIDED RAPID SYMPTOM RELIEF. WHEN ADMINISTERED BEFORE A TEST MEAL, FAMOTIDINE REDUCED SYMPTOMS THAT WOULD OTHERWISE HAVE BEEN EXPECTED.

AFTER ORAL ADMINISTRATION, A DOSE-RESPONSE RELATIONSHIP WAS CLEARLY DEMONSTRATED FROM 0.5 AND 10 MG FAMOTIDINE IN TERMS OF RAISING GASTRIC PH BETWEEN AND AFTER MEALS. FAMOTIDINE DOSES OF 2.5 TO 10 MG WERE DEMONSTRATED TO PRODUCE A STATISTICALLY SIGNIFICANT EFFECT OF GASTRIC PH AS COMPARED TO PLACEBO. THE ONSET OF EFFECT FOR THE 5 AND 10 MG DOSES WERE SEEN AT APPROXIMATELY 1.5 HOURS POSTDOSE WHILE THAT OF THE 2.5 MG DOSE WAS NOT SEEN UNTIL 2.5 HOURS POSTDOSE. THE MAXIMUM EFFECT, AS MEASURED BY PEAK MEAN PH VALUE, OCCURRED AT 3.5 HOURS. THE ACTIVITY OF THE 5 AND 10 MG DOSES CONTINUED UNTIL APPROXIMATELY 9 HOURS POSTDOSE. FAMOTIDINE IS WELL-TOLERATED AT THESE DOSE LEVELS.

SYSTEMIC EFFECTS OF 'BLOCAZIDE' IN THE CNS, CARDIOVASCULAR, RESPIRATORY OR ENDOCRINE SYSTEMS WERE NOT NOTED IN CLINICAL PHARMACOLOGY STUDIES. ALSO, NO ANTI-ANDROGENIC EFFECTS WERE NOTED IN CLINICAL PHARMACOLOGY STUDIES. SERUM HORMONE LEVELS, INCLUDING PROLACTIN, CORTISOL, THYROXINE (T_4), AND TESTOSTERONE, WERE NOT ALTERED AFTER TREATMENT WITH 'BLOCAZIDE'.

15. Pharmacokinetic particulars:

'BLOCAZIDE' OBEYS LINEAR KINETICS.

IN PHARMACOKINETIC STUDIES IN THE ELDERLY, NO CLINICALLY SIGNIFICANT AGE-RELATED CHANGES WERE DETECTED.

COMPARED TO HISTORICAL DATA FROM YOUNGER SUBJECTS, AGE DOES NOT APPEAR TO AFFECT THE BIOAVAILABILITY OF SINGLE DOSES OF FAMOTIDINE; HOWEVER, THE ELIMINATION APPEARS TO BE REDUCED IN ELDERLY SUBJECTS COMPARED WITH YOUNGER SUBJECTS.

'BLOCAZIDE' IS RAPIDLY ABSORBED WITH DOSE-RELATED PEAK PLASMA CONCENTRATIONS OCCURRING AT 1-3 HOURS. THE MEAN BIOAVAILABILITY OF AN ORAL DOSE IS 40-45%. BIOAVAILABILITY IS NOT CLINICALLY AFFECTED BY THE PRESENCE OF FOOD IN THE STOMACH. 'BLOCAZIDE' UNDERGOES MINIMAL FIRST-PASS METABOLISM. REPEATED DOSES DO NOT LEAD TO ACCUMULATION OF THE DRUG.

PROTEIN BINDING IN THE PLASMA IS RELATIVELY LOW (15-20%). THE PLASMA HALF-LIFE AFTER A SINGLE ORAL DOSE OR MULTIPLE REPEATED DOSES (FOR 5 DAYS) WAS APPROXIMATELY 3 HOURS.

METABOLISM OF THE DRUG OCCURS IN THE LIVER, WITH FORMATION OF THE INACTIVE SULPHOXIDE METABOLITE.

FOLLOWING ORAL ADMINISTRATION, THE MEAN URINARY EXCRETION OF THE ABSORBED DOSE OF FAMOTIDINE IS 65-70%. OF THE TOTAL ORAL DOSE ADMINISTERED, 25-30% IS RECOVERED AS UNCHANGED COMPOUND IN THE URINE. RENAL CLEARANCE IS 250-450 ML/MIN, INDICATING SOME TUBULAR EXCRETION. A SMALL AMOUNT MAY BE EXCRETED AS THE SULPHOXIDE.

A 10 MG CHEWABLE TABLET 'BLOCAZIDE' WAS FOUND TO BE BIOEQUIVALENT TO A 10 MG FILM-COATED TABLET 'BLOCAZIDE'.

Date: *24 JANUARY 1993*

L	1						/										

16. Name(s) of manufacturers and site(s) of manufacture of (a) the active substance(s) and (b) the dosage form

(a) The active substance(s)

YAMANOUCHI IRELAND CO LTD
DAMASTOWN, MULHADDART
DUBLIN 15
IRELAND

OR

(CONTINGENT SOURCE)
YAMANOUCHI PHARMACEUTICAL CO LTD
NO. 1-8, AZUSAWAL-CHOME
ITABASHI-KU, TOKYO, 174, JAPAN

(b) The dosage form

WOELM PHARMA GMBH
MAX-WOELM-STRASSE, 3440 ESCHWEGE
GERMANY

OR

MERCK MANUFACTURING DIVISION
MERCK SHARP & DOHME LIMITED
SHOTTON LANE, CRAMLINGTON
NORTHUMBERLAND, NE23 9JU

OR

MERCK MANUFACTURING DIVISION
MERCK SHARP & DOHME (ITALIA) SPA
VIA EMILIA 21, 27100 PAVIA
ITALY

17. Assembler(s):

BLISTER PACKS

AS THE MANUFACTURERS OF THE DOSAGE FORM

BOTTLE PACKS

MERCK MANUFACTURING DIVISION
MERCK SHARP & DOHME BV
WAARDERWEG 39, HAARLEM, NETHERLANDS

18. Importer:

MERCK MANUFACTURING DIVISION
MERCK SHARP & DOHME LIMITED
SHOTTON LANE
CRAMLINGTON
NORTHUMBERLAND
NE23 9JU

19. Site and arrangements for quality control:

FULL QUALITY CONTROL TESTING WILL BE PERFORMED AT THE SITE OF MANUFACTURE. IMPORTED MATERIAL WILL BE ACCOMPANIED BY ANALYTICAL PROTOCOLS; IDENTITY TESTING WILL BE CARRIED OUT ON IMPORTED MATERIAL AT MSD, CRAMLINGTON.

20. Distributor (where applicable)

MERCK SHARP & DOHME LIMITED, CRAMLINGTON.

21. List other countries of registration:

FAMOTIDINE TABLETS, 20 AND 40 MG ARE REGISTERED IN MOST COUNTRIES WORLDWIDE FOR PRESCRIPTION USE. APPLICATION FOR OVER-THE-COUNTER USE OF THE 10 MG STRENGTH TABLET WILL BE MADE IN A NUMBER OF COUNTRIES E.G. AUSTRIA, BELGIUM, DENMARK, FRANCE, SWITZERLAND, SWEDEN, USA ETC.

Date: *24 JANUARY 1993*

Introduction

Famotidine (MK-0208, YM-11170, L-643,341) is a highly potent gastric H_2-receptor antagonist. It inhibits gastric acid secretion and accelerates healing of peptic ulcers and is approved for the treatment of active gastric and duodenal ulcers and for maintenance therapy for duodenal ulcer patients. It has been marketed for these indications in many countries around the world for several years.

The nonclinical pharmacology of famotidine has been well characterized in several in vivo and in vitro systems. It has no significant effects on other major organ systems. The absorption, metabolism, and excretion of famotidine were studied in rats and dogs. It is well absorbed from the gastrointestinal tract and the only metabolite (sulfoxide) was present in minor amounts. These data have been submitted as part of preclinical data supporting oral and intravenous administration in man.

The safety of famotidine has been extensively evaluated in laboratory animals and in several in

Introduction (continued)

vitro systems and the detailed study reports have been submitted as part of the original application for marketing the tablet. No additional studies have been done since 1985. The objective of the present review is to briefly summarize prior preclinical information to support marketing of famotidine over the counter. The preclinical safety of famotidine is only briefly reviewed here. References to the respective sections of the original submission can easily be made. A full list of studies is attached (Attachment 1).

Single Dose Toxicity

Famotidine was found to be relatively non-toxic based on single dose toxicity studies in rats, mice, and dogs. The oral LD_{50} was greater than 8 g/kg and the LD_{50} by parenteral routes was greater than 254 mg/kg.

Repeated Dose Toxicity

Rats and dogs tolerated repeated-dose oral administration of famotidine for up to one year at doses up to 2 g/kg/day in rats and up to 1 g/kg/day in

Repeated Dose Toxicity (continued)

dogs. Intravenous administration was also well tolerated by rats for 13 weeks at dosage levels up to 20 mg/kg/day and by dogs, except for occasional emesis, at dosage levels up to 10 mg/kg/day for 26 weeks. In rat studies there was a dose- and time-dependent increase in the incidence and, to some extent, the severity of eosinophilic cytoplasmic granularity (ECG) of gastric chief cells compared to controls. Similar ECG of gastric chief cells had been seen in rats treated with compounds having similar pharmacologic activity and this change was fully reversible with discontinuation of treatment. A similar change has not been seen in mice or dogs. This change is considered to be of no toxicologic significance.

Developmental and Reproductive Toxicity

Famotidine was tested to assess its teratogenic potential in rats and rabbits and its effect on fertility and reproduction and peri- and postnatal development in rats. No alteration in reproductive

Developmental and Reproductive Toxicity (continued)

parameters and no evidence of teratogenicity were seen in rats and rabbits given high doses of famotidine by oral and intravenous routes. Fetotoxicity was seen but only at maternotoxic doses.

Genetic Toxicity

The results of extensive in vitro and in vivo studies using mammalian and non-mammalian systems indicates that there is no genotoxic risk associated with famotidine.

Carcinogenicity

Studies were performed in rats (106 weeks) and mice (92 weeks) at very high doses to evaluate the carcinogenic potential of famotidine. These studies did not indicate any treatment-related increased tumor incidence.

Special Toxicity

The safety of famotidine was tested with regard to its effects on the thyroid, eye, and injection site and immunogenic and hemolytic potential. These studies

Special Toxicity (continued)

did not show any effect on the thyroid of rats and no immunogenicity in mice or guinea pigs. Famotidine was non-irritating to the rabbit eye and intravenous injection site. Famotidine also did not cause hemolysis of human and rabbit erythrocytes.

Conclusion

The safety of famotidine has been extensively evaluated in in vivo studies in laboratory animals and in several in vitro studies at doses that are very high relative to the clinical dose. There are no findings of any toxicologic significance. Furthermore, famotidine as a prescription product has been used extensively for the treatment of active gastric and duodenal ulcers and as maintenance therapy for duodenal ulcer patients for several years. The dosages used were consistently higher than the dose which is being proposed for OTC use. There are no preclinical safety issues which would preclude the use of the compound as a self medication in the general population.

Famotidine OTC

Abbreviated Expert Report on the Nonclinical Pharmacology and Toxicology Documentation

Famotidine (MK-0208, YM-11170 or L-643,341) is a widely used highly potent gastric H_2-antagonist. Famotidine tablets and an intravenous formulation have been approved for the treatment of active gastric and duodenal ulcers for several years. An application is now being submitted for over the counter (OTC) use of a lower dose famotidine tablet.

The original application included a full account of the preclinical data supporting the oral and intravenous administration. No further preclinical studies were done since the original submission. Therefore, this will be an abbreviated review of preclinical information.

The pharmacodynamics and pharmacokinetics of famotidine were studied using well accepted test systems. These pharmacodynamic studies showed that famotidine is a potent, competitive H_2-antagonist with little other pharmacologic action. The absorption, metabolism and excretion studies were done in the rat and dog. The drug is well absorbed orally and excreted predominantly in the urine as unchanged drug. There is no change in the metabolism or accumulation following repeated daily dosing.

The general toxicity of famotidine following single and repeated oral and intravenous dosing has been studied in several laboratory animal species. These studies employed well accepted study design with appropriate numbers of animals and evaluated multiple antemortem and postmortem parameters. The doses used in these studies were very large relative to the maximum intended clinical dose. Overall, famotidine had

a very low order of toxicity. This is evidenced by the very large oral LD_{50} (>8 g/kg) and by the lack of any significant toxicity in rats at doses up to 2000 mg/kg/day and in dogs at doses up to 1000 mg/kg/day for one year.

Extensive series of studies to assess the reproductive toxicity, genetic toxicity and carcinogenicity of famotidine were done using well accepted in vivo and in vitro studies. These studies clearly demonstrated that famotidine is not teratogenic, genotoxic or carcinogenic.

In conclusion, the safety of famotidine has been clearly established in preclinical studies. Furthermore, famotidine as a prescription product (oral and IV) has been used extensively for the treatment of active gastric and duodenal ulcers for many years. The doses used were consistently higher than the dose which is being proposed for OTC use. Therefore, no additional toxicity studies are needed prior to the projected human use as an OTC product. There are no preclinical issues which would preclude the use of the compound as a self medication in the general population.

ID1632/kmc

[redacted] 55

APPENDIX B

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV B OF THE DOSSIER TABLE 1 OF 15 REFERENCE 1 VOL 2 PAGE 20000 TO 20078	

STUDY TITLE: A Double-Blind, Randomized, Placebo-Controlled Trial to Investigate the Pharmacodynamics of Famotidine 0.5, 2.5, 5 and 10 mg Tablets #016

INVESTIGATOR/SITE: [redacted] Miami, FL, U.S.A.

STUDIED PERIOD: Mar. 89 to Apr. 89 | **CLINICAL PHASE:** I

DURATION: A 5-period study. Each subject received each dosage level or placebo. Gastric pH was monitored over 24 hours, with at least a 6-day washout between treatments.

OBJECTIVES: 1) To show a dose-response inhibition of gastric acid secretion. 2) To gather information on the safety and tolerability of oral doses of famotidine.

METHODOLOGY: Double-blind, placebo-controlled, 5-period, randomized, crossover study in 10 healthy subjects

NUMBER OF SUBJECTS: 10, ages 23 to 44

DIAGNOSIS/INCLUSION CRITERIA: Healthy male nonsmoking subjects between the age of legal consent and 45 years and weighing within 15% of ideal body weight for age and height.

DOSAGE/BATCH NOS.:

Dosage	Dosage Form	Strength	Clinical Lot No.	Formulation No.
Famotidine	FCT	0.5 mg	C-T378	0208FCT030J001
Famotidine	FCT	2.5 mg	C-T378	0208FCT001H002
Famotidine	FCT	5.0 mg	C-T378	0208FCT001A001
Famotidine	FCT	10.0 mg	C-T378	0208FCT011D003
Placebo matching famotidine	FCT	--	C-T378	P0208FCT031A001

EVALUATION CRITERIA: Following the placement of the pH probes, a standard high protein meal was consumed. One hour after eating this meal the subject received the study drug. Additional standardized meals were given at 3 and 9 hours postdose. Gastric pH was measured continuously (at 4 sec intervals) over 24 hours, and expressed as mean pH for each interval.

STATISTICAL METHODS: Analysis of variance (ANOVA) for a 5-period, crossover design was performed for pH at each 10-minute averaged interval. The ANOVA model included terms for subject, day (=period), and treatment. Maximum pH, and maximum pH change from pre-meal baseline, after each meal were also analyzed using the same method.

SUMMARY—CONCLUSIONS: (1) Famotidine (2.5 to 10 mg) is more effective than placebo as an inhibitor of gastric acid secretion; (2) Famotidine in the range of 0.5 to 10 mg exhibits a dose-response relationship for the inhibition of gastric acid secretion; (3) The threshold dose of famotidine when given orally, appears to be between 0.5 and 2.5 mg; (4) The duration of effect on gastric pH for the 5 and 10 mg doses is approximately 9 hours; and (5) Single oral doses of famotidine in the range of 0.5 to 10 mg are well tolerated.

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV B OF THE DOSSIER TABLE 2 OF 15 REFERENCE 5 VOL 2 PAGE 20297 TO 20472	

STUDY TITLE: 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 #017-01

INVESTIGATOR/SITE: Twenty-nine investigators in the U.S. enrolled patients.

STUDIED PERIOD: Oct. 89 to Nov. 90 | **CLINICAL PHASE:** II

DURATION: One-week single-blind baseline phase and a 4-week double blind phase.

OBJECTIVES: 1) Assess the efficacy of famotidine vs. placebo in relief of heartburn. 2) Assess the efficacy of antacid vs. placebo in relief of heartburn. 3) Assess effects on underlying diseases of the upper gastrointestinal tract by performing pre- and posttreatment upper gastrointestinal endoscopy. 4) Estimate the prevalence of esophageal motility disorders and assess effects on questionable or abnormal esophageal motility.

METHODOLOGY: Double-blind, randomized, placebo-controlled, parallel group study of famotidine and antacid

NUMBER OF SUBJECTS: Baseline Phase - A total of 792 patients entered the baseline phase. Two hundred twenty-seven (227) of these patients were discontinued; 565 patients entered the double-blind phase. Ages 18 to 81.

DIAGNOSIS/INCLUSION CRITERIA: Males and females at least 18 years with a history of heartburn, who self-medicate with antacid at least three times per week.

DOSAGE/BATCH NOS.:

Dosage	Formulation Nos.	Dosage	Formulation Nos.
Famotidine Placebo	P0208FCT031A002	Antacid Placebo	P0208FCT029I002
Famotidine 5 mg	0208FCT001A001	Antacid	C0208FCT028I002
Famotidine 10 mg	0208FCT011D003	Wingel® (Backup Medication)	LOT601EC, LOT601ED
Famotidine 20 mg	0208FCT033B001		

EVALUATION CRITERIA: Patients' global assessment of 28 days of treatment and patients' response to treatment at 1, 2 and 3 hours after each dose of test medication.

STATISTICAL METHODS: Global evaluation, proportion of episodes relieved, proportion of episodes requiring backup medication, and proportion of episodes requiring remedication by logistic regression using SAS, PROC LOGISTIC; the model included terms for treatment, investigator, baseline episode severity, and baseline number of episodes. Number of heartburn episodes: likelihood ratio test based on Poisson PHGLM; the model included terms for treatment, investigator, and initial episode severity. Sample size n=85 patients per group has 80% power to detect a 25% difference in proportion of episodes relieved between placebo and active treatment (at α=0.5, two-tailed).

SUMMARY—CONCLUSIONS: 1) Famotidine is more effective in relieving heartburn than placebo. 2) Antacid relieves heartburn more effectively than placebo. 3) There is no consistent evidence that famotidine relieves heartburn more effectively than antacid. 4) There is no consistent evidence of a dose response for famotidine. 5) Famotidine doses of 5 mg, 10 mg, and 20 mg are well-tolerated by the patient population tested in this study. 6) None of the treatments lead to deterioration in underlying disorders of the upper gastrointestinal mucosa or of esophageal motility.

APPENDIX B

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV B OF THE DOSSIER TABLE 3 OF 15 REFERENCE 6 VOL 2 PAGE 20473 TO 20602	

STUDY TITLE: 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 #019-00

INVESTIGATOR/SITE: Twenty-three U.S. study sites

STUDIED PERIOD: Dec. 89 to Jan. 91 | **CLINICAL PHASE:** II

DURATION: One week in baseline phase and 4 weeks in double-blind phase.

OBJECTIVES: 1) To assess the efficacy of famotidine vs. placebo and antacid vs. placebo in relief of heartburn. 2) To preliminarily assess when heartburn recurs after successful treatment.

METHODOLOGY: Double-blind, randomized, placebo-controlled, parallel group study of famotidine and antacid

NUMBER OF SUBJECTS: Baseline Phase - A total of 749 patients entered the baseline phase. Of these patients, 240 were discontinued during baseline phase and 509 were randomized into the double-blind phase. Ages 18 to 83.

DIAGNOSIS/INCLUSION CRITERIA: Male or female patients, age 18 years or older, with a history of heartburn requiring self-medication with antacid three or more times per week.

DOSAGE/BATCH NOS.: PRN up to twice daily (p.o.) during 1-week baseline phase and 4-week double-blind phase.

Dosage	Formulation Nos.
Famotidine Placebo:	P0208FCT031A003, P0208FCT031A005
Famotidine 10 mg:	0208FCT011D003
Famotidine 20 mg:	0208FCT033B002, 0208FCT033B004
Antacid Placebo:	P0208FCT029I003, P0208FCT029I005
Antacid:	C0208FCT028I003, C0208FCT028I006
Backup Medication (Wingel®):	Lot 601EC, Lot 601ED, Lot 602FA

EVALUATION CRITERIA: Patients provided global assessments of 28 days of treatment and their responses to treatment at 1/4, 1/2, 1, 1 1/2, 2, 3, 4, and 5 hours after the first dose of double-blind medication, and their responses at 1, 2, 3, 4 and 5 hours after subsequent doses of double-blind test medication.

STATISTICAL METHODS: Logistic regression on global evaluation, proportion of episodes relieved, proportion of episodes requiring backup medication, and proportion of episodes requiring remedication using SAS, PROC LOGISTIC. The model included terms for treatment, investigator, baseline episode severity, and baseline number of episodes. Likelihood ratio test based on Poisson distribution for number of heartburn episodes. Survival analysis on time to relief of first episode using SAS, PROC PHGLM. The model included terms for treatment, investigator, and initial episode severity. A sample size of n=85 patients per group has 80% power to detect a 25% difference in proportion of episodes relieved between placebo and active treatment (at α=0.5, two-tailed).

XPROJECT.1630/3/07DEC92

APPENDIX B

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV OF THE DOSSIER TABLE 3 OF 15 REFERENCE 6 VOL 2 PAGE 20473 TO 20602 Supplementary Page 2	

SUMMARY—CONCLUSIONS: 1) Famotidine is more effective in relieving heartburn than placebo. 2) Antacid relieves heartburn more effectively than placebo. 3) There is no consistent evidence that famotidine relieves heartburn more effectively than antacid. 4) There is no consistent evidence of a dose response. 5) Famotidine doses of 10 mg and 20 mg are well-tolerated by the patient population tested in this study.

XPROJECT.1630/4/07DEC92

APPENDIX 8

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV B OF THE DOSSIER TABLE 4 OF 15 REFERENCE 7 VOL 2 PAGE 20603 TO 20655	

STUDY TITLE: A Double-Blind, Crossover Trial to Determine Efficacy and Tolerability of Famotidine 5 mg, 10 mg and 20 mg vs. Placebo in Prevention of Symptoms Produced by a Test Meal #020

INVESTIGATOR/SITE: [redacted] Boston, MA U.S.A.

STUDIED PERIOD: Oct. 89 to Nov. 89 | **CLINICAL PHASE:** II

DURATION: Screening test meal, then a treatment phase of four provocative meals with approximately 7 days between meals.

OBJECTIVES: 1) To compare the efficacy of famotidine 5 mg, 10 mg and 20 mg vs. placebo in prevention of heartburn, acid indigestion or sour stomach or upset stomach and overall discomfort produced by a test meal. 2) To compare the efficacy of famotidine 10 and 20 mg vs. famotidine 5 mg in prevention of heartburn, acid indigestion or sour stomach or upset stomach and overall discomfort produced by a test meal.

METHODOLOGY: Double-blind, randomized, placebo controlled, four-way crossover study of famotidine with patients receiving study dose 1 hour prior to the test meal

NUMBER OF SUBJECTS: 121, ages 20 to 61

DIAGNOSIS/INCLUSION CRITERIA: Age 18 or older with at least a 2-month history of heartburn, acid indigestion or sour/upset stomach occurring 3 times per week

DOSAGE/BATCH NOS.:

	Dosage	Formulation Nos.
MK-208	5 mg	0208 FCT001A001
	10 mg	0208 FCT011D003
	20 mg	0208 FCT033B001
Placebo	—	P0208 FCT031A001
Maalox TC	28 mEq	83278

Treatment medication taken 1 hour before test meal. Maalox TC used as a rescue medication was available for patients that developed symptoms of moderate or greater severity.

EVALUATION CRITERIA: Categorical assessment on a six-point scale for upper gastrointestinal discomfort beginning immediately before each test meal and every 15 minutes thereafter for 5 hours. Global assessment on a five-point categorical scale by the patient on how well the drug worked to be asked prior to rescue medication or at the end of each treatment session.

STATISTICAL METHODS: Global evaluations, peak heartburn, acid/sour stomach, overall discomfort, and use of rescue medication by logistic regression using SAS, PROC LOGIST. Areas Under the Curve (AUC) for heartburn, acid/sour stomach, and overall discomfort by parametric linear models using SAS, PROC GLM. Time to rescue medication by survival analysis using SAS, PROC PHGLM. All the above models included factors for treatment, period, patient and

APPENDIX B

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV OF THE DOSSIER TABLE 4 OF 15 REFERENCE 7 VOL 2 PAGE 20603 TO 20655 Supplementary Page 2	

STATISTICAL METHODS (CONT.): crossover. A sample size of n=100 patients per group has a 95% power (depending on the correlation between responses across periods) to detect a 25% difference between placebo and active treatment in the proportion of patients with "moderate" or worse heartburn 75 minutes after having a test meal (at α=0.5, two-tailed).

SUMMARY—CONCLUSIONS: 1) Administered 1 hour before a test meal, famotidine doses of 5, 10, and 20 mg are more effective than placebo in preventing upper gastrointestinal symptoms produced by food and beverage: global assessments are more favorable; heartburn is less severe; overall discomfort and acid/sour stomach is less severe; and open-label antacid is required less frequently after the test meal. 2) There are no differences in efficacy among the famotidine doses tested. 3) Doses of 5 mg, 10 mg and 20 mg of famotidine are well-tolerated by patients with a history of heartburn, acid indigestion, or sour/upset stomach.

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV B OF THE DOSSIER TABLE 5 OF 15 REFERENCE 2 VOL 2 PAGE 20079 TO 20151	

STUDY TITLE: A Double-Blind, Nine-Period, Placebo-Controlled, Crossover Study to Investigate the Effect of Varying Strengths of Antacids on the Pharmacodynamics of Flavored Famotidine Power #021

INVESTIGATOR/SITE: [redacted], Miami, FL, U.S.A.

STUDIED PERIOD: Jan. 90 to Mar. 90 | **CLINICAL PHASE:** I

DURATION: Nine periods involving a single dose of study drug followed by monitoring gastric pH for 12 hours and a 72-hour washout between treatments

OBJECTIVES: 1) To compare the pharmacokinetics of famotidine on the presence and absence of concomitant antacid (MYLANTA II, aluminum hydroxide) intake. 2) To compare the effect of antacids on the pharmacokinetics and pharmacodynamics to famotidine at doses of 10 and 20 mg. 3) To evaluate the safety and tolerability of famotidine.

METHODOLOGY: A single-center, double-blind, placebo-controlled, 9-period, crossover study in 18 healthy male subjects. Design balanced for carryover effects.

NUMBER OF SUBJECTS: 20, ages 22 to 44

DIAGNOSIS/INCLUSION CRITERIA: Healthy male subjects between the age of legal consent and 45 years and weighing within 15% of their ideal body weight.

DOSAGE/BATCH NOS.:

	Dosage Form	Strength	Formulation Numbers
Famotidine (F)	Powder	10 mg	0208 OP0055C001
Famotidine	Powder	20 mg	0208 OP0054B001
Famotidine placebo	Powder	—	PO 208 OP0056A001
MYLANTA II (M)	Chewable tablets	23 mEq	CO208 AOTC002A003
Antacid placebo	Chewable tablets	—	PO 208 AOTC005A002

EVALUATION CRITERIA: Plasma was assayed for famotidine at various times posttreatment. Gastric pH was measured every 4 seconds for 12 hours. Routine hematology, chemistry, and urinalysis was performed pre- and poststudy for safety assessment.

STATISTICAL METHODS: Analysis of variance (ANOVA) for a 9-period, crossover model was performed for pH at each 10-minute timepoint. The treatment effect was assessed as a 3 x 3 factorial design consisting of famotidine effect, the number of tablets of antacid effect, and the famotidine-by-antacid effect. Since the pharmacokinetic data were imbalanced with period and carryover, a multifactor ANOVA with subjects and treatment as factors was used. Also, 90% confidence intervals for geometric mean ratio of AUC were computed..

SUMMARY—CONCLUSIONS: 1) Famotidine 10 to 20 mg as a single-dose increases gastric pH in a dose-related fashion. One or 2 tablets of MYLANTA II does not interfere with this effect. 2) The pharmacokinetics of famotidine over the range of 10 to 20 mg are not affected by the coadministration of MYLANTA II up to 46 mEq of ANC = (2 tablets). 3) Single doses of famotidine powder 10 and 20 mg alone or in combination with MYLANTA II, 1 and 2 tablets, appears to be well-tolerated in healthy male volunteers.

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV B OF THE DOSSIER TABLE 6 OF 15 REFERENCE 8 VOL 3 PAGE 20656 TO 20725	

STUDY TITLE: A Double-Blind, Crossover Trial to Evaluate the Efficacy and Safety of Famotidine in the Prevention of Food Induced Symptoms #022

INVESTIGATOR/SITE: [redacted] Houston, TX U.S.A.

STUDIED PERIOD: Dec. 89 to Feb. 90 | **CLINICAL PHASE:** II

DURATION: Screening test meal, then a treatment phase of four provocative meals with approximately 4-16 days between all meals.

OBJECTIVES: 1) To compare the efficacy of famotidine 5 mg, 10 mg and 20 mg vs. placebo in prevention of heartburn, acid indigestion or sour stomach or upset stomach, and overall discomfort produced by a test meal. 2) To compare the efficacy of famotidine 10 mg and 20 mg vs. famotidine 5 mg in prevention of heartburn, acid ingestion or sour stomach or upset stomach, and overall discomfort product by a test meal.

METHODOLOGY: Double-blind, randomized, placebo controlled, four-way crossover study of famotidine with patient receiving study dose immediately prior to the test meal

NUMBER OF SUBJECTS: 105, ages 21 to 64

DIAGNOSIS/INCLUSION CRITERIA: Age 21 or older with at least a 2-month history of heartburn, acid indigestion or sour/upset stomach occurring 3 times per week

DOSAGE/BATCH NOS.:

	Dosage	Formulation Nos.
MK-208	5 mg	0208 FCT001A001
	10 mg	0208 FCT011D003
	20 mg	0208 FCT033B001
Placebo	—	P0208 FCT031A001
Maalox TC	28 mEq	83278

Treatment medication taken immediately prior to the test meal. Maalox TC used as a rescue medication was available for patients that developed symptoms of moderate or greater severity.

EVALUATION CRITERIA: Categorical assessment on a six-point scale for upper gastrointestinal discomfort beginning immediately before each test meal and every 15 minutes thereafter for 5 hours. Global assessment on a five-point categorical scale by the patient on how well the drug worked to be asked prior to rescue medication or at the end of each treatment session.

STATISTICAL METHODS: Global evaluation, peak heartburn, acid/sour stomach, overall discomfort, and use of rescue medication by logistic regression using SAS, PROC LOGIST. Areas under the curve (AUC) for heartburn, acid/sour stomach, and overall discomfort by parametric linear models using SAS, PROC GLM. Time to rescue medication by survival analysis using SAS, PROC PHGLM. All the above models included factors for treatment, period, patient, and

APPENDIX B

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV OF THE DOSSIER TABLE 6 OF 15 REFERENCE 8 VOL 3 PAGE 20656 TO 20725 Supplementary Page 2	

STATISTICAL METHODS (CONT.): carryover. A sample size of n=100 patients has approximately 95% power (depending on the correlation between responses across periods) to detect a 25% difference between placebo and active treatment sin the proportion of patients with "moderate" or worse heartburn 75 minutes after having a test meal (at α=0.05, two-tailed).

SUMMARY—CONCLUSIONS: 1) In this study, there was no clear demonstration that famotidine administered immediately prior to a test meal prevents upper gastrointestinal symptoms induced by food and beverage. a) There were differences in response among famotidine 5 and 10 mg and placebo, but the size of the drug effect strongly depended on the sequence in which drugs were administered. In particular, the most favorable efficacy scores occur with the famotidine 5 or 10 mg doses in the period following administration of placebo in the previous period. b) After adjusting for the carryover effect described above and reviewing the results of the first period data, famotidine doses of 5 mg and 10 mg appear to be more effective than placebo. However, famotidine 20 mg was similar to placebo, and famotidine 5 mg and 10 mg were superior to 20 mg in some measures. 2) Doses of 5 mg, 10 mg and 20 mg are well-tolerated by the patient population tested in this study.

XPROJECT.1630/9/07DEC92

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV B OF THE DOSSIER TABLE 7 OF 15 REFERENCE 9 VOL 3 PAGE 20726 TO 20781	

STUDY TITLE: A Double-Blind, Crossover Trial to Evaluate the Safety and Efficacy of Famotidine in the Prevention of Symptoms Induced by a Provocative Meal #024

INVESTIGATOR/SITE: [redacted] Miami, FL U.S.A.

STUDIED PERIOD: Jan. 90 to Apr. 90 | **CLINICAL PHASE:** II

DURATION: Screening test meal, then a treatment phase of four provocative meals with approximately 4-16 days between all meals.

OBJECTIVES: 1) To compare the efficacy of famotidine 5 mg, 10 mg and 20 mg vs. placebo in prevention of heartburn, acid indigestion or sour stomach or upset stomach, and overall discomfort produced by a test meal. 2) To compare the efficacy of famotidine 10 and 20 mg vs. famotidine 5 mg in prevention of heartburn, acid ingestion or sour stomach or upset stomach, and overall discomfort product by a test meal.

METHODOLOGY: Double-blind, randomized, placebo controlled, four-way crossover study of famotidine with dosing immediately prior to provocative meal

NUMBER OF SUBJECTS: 102, ages 18 to 69

DIAGNOSIS/INCLUSION CRITERIA: Age 18 or older with at least a 2-month history of heartburn, acid indigestion or sour/upset stomach occurring 3 times per week

DOSAGE/BATCH NOS.:

	Dosage	Formulation Nos.
MK-208	5 mg	0208 FCT001A001
	10 mg	0208 FCT011D003
	20 mg	0208 FCT033B001
Placebo	—	P0208 FCT031A001
Maalox TC	28 mEq	83278

Treatment medication taken immediately prior to the test meal. Maalox TC used as a rescue medication was available for patients that developed symptoms of moderate or greater severity.

EVALUATION CRITERIA: Categorical assessment on a six-point scale for upper gastrointestinal discomfort beginning immediately before each test meal and every 15 minutes thereafter for 5 hours. Global assessment on a five-point categorical scale by the patient on how well the drug worked to be asked prior to rescue medication or at the end of each treatment session.

STATISTICAL METHODS: Global evaluations, peak heartburn, acid/sour stomach, overall discomfort, and use of rescue medication by logistic regression using SAS, PROC LOGIST. Areas under the curve (AUC) for heartburn, acid/sour stomach, and overall discomfort by parametric linear models using SAS, PROC GLM. Time to rescue medication by survival analysis using SAS, PROC PHGLM. All the above models included factors for treatment, period, patient, and carryover. A sample size of n=100 patients has approximately 95% power

APPENDIX B

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV OF THE DOSSIER TABLE 7 OF 15 REFERENCE 9 VOL 3 PAGE 20726 TO 20781 Supplementary Page 2	

STATISTICAL METHODS (CONT.): (depending on the correlation between responses across periods) to detect a 25% difference between placebo and active treatment in the proportion of patients with "moderate" or worse heartburn 75 minutes after having a test meal (at α=0.05, two-tailed).

SUMMARY—CONCLUSIONS: 1) in this study, there was no clear evidence that famotidine administered immediately prior to a test meal prevents upper gastrointestinal symptoms produced by meal and beverage. Although famotidine doses of 5, 10 mg and 20 mg are more effective than placebo as measured by global evaluation, this result was not accompanied by significant decreases in heartburn severity, acid/sour stomach severity, overall discomfort, or need for antacid rescue. 2) Doses of 5 mg, 10 mg and 20 mg of famotidine are well-tolerated by patients with a history of heartburn, acid indigestion, or sour/upset stomach.

XPROJECT.1630/11/07DEC92

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV B OF THE DOSSIER TABLE 8 OF 15 REFERENCE 10 VOL 3 PAGE 20782 TO 20839	

STUDY TITLE: A Double-Blind, Crossover Trial to Determine the Efficacy and Tolerability of Famotidine in the Prevention of Symptoms Induced by a Test Meal #025

INVESTIGATOR/SITE: [redacted] Rockville Center, NY U.S.A.

STUDIED PERIOD: Feb. 90 to Mar. 90 | **CLINICAL PHASE:** II

DURATION: Screening test meal, then a treatment phase of four provocative meals with approximately 4-16 days between all meals.

OBJECTIVES: 1) To compare the efficacy of famotidine 5 mg, 10 mg and 20 mg vs. placebo in prevention of heartburn, acid indigestion or sour stomach or upset stomach, and overall discomfort produced by a test meal. 2) To compare the efficacy of famotidine 10 mg and 20 mg vs. famotidine 5 mg in prevention of heartburn, acid ingestion or sour stomach or upset stomach, and overall discomfort product by a test meal.

METHODOLOGY: Double-blind, randomized, placebo controlled, four-way crossover study of famotidine with dosing 1 hour prior to provocative meals

NUMBER OF SUBJECTS: 105, ages 18 to 65

DIAGNOSIS/INCLUSION CRITERIA: Age 18 or older with at least a 2-month history of heartburn, acid indigestion or sour/upset stomach occurring 3 times per week

DOSAGE/BATCH NOS.:

	Dosage	Formulation Nos.
MK-208	5 mg	0208 FCT001A001
	10 mg	0208 FCT011D003
	20 mg	0208 FCT033B001
Placebo	---	P0208 FCT031A001
Maalox TC	28 mEq	83278

Treatment medication taken 1 hour before test meal. Maalox TC used as a rescue medication was available for patients that developed symptoms of moderate or greater severity.

EVALUATION CRITERIA: Categorical assessment on a six-point scale for upper gastrointestinal discomfort beginning immediately before each test meal and every 15 minutes thereafter for 5 hours. Global assessment on a five-point categorical scale by the patient on how well the drug worked to be asked prior to rescue medication or at the end of each treatment session.

STATISTICAL METHODS: Global evaluation, peak heartburn, acid/sour stomach, overall discomfort, and use of rescue medication by logistic regression using SAS, PROC LOGIST. Areas under the curve (AUC) for heartburn, acid/sour stomach, and overall discomfort by parametric linear models using SAS, PROC GLM. Time to rescue medication by survival analysis using SAS, PROC PHGLM. All the above models included factors for treatment, period, patient, and

APPENDIX B

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV OF THE DOSSIER TABLE 8 OF 15 REFERENCE 10 VOL 3 PAGE 20782 TO 20839 Supplementary Page 2	

STATISTICAL METHODS (CONT.): carryover. A sample size of n=100 patients has approximately 95% power (depending on the correlation between responses across periods) to detect a 25% difference between placebo and active treatment sin the proportion of patients with "moderate" or worse heartburn 75 minutes after having a test meal (at α=0.05, two-tailed).

SUMMARY—CONCLUSIONS: 1) The overall pattern of response provides an equivocal demonstration of drug effect: a) Famotidine 10 mg and 20 mg were superior to placebo as measured by Global Evaluation. For the famotidine 10 mg dose only, this was accompanied by reductions in Peak Heartburn scores and Mean Area Under the Curve for heartburn, acid/sour stomach and overall discomfort. b) Famotidine 5 mg was found to be similar to placebo. c) An observed carryover effect complicates the interpretation of the significant differences from placebo with respect to the frequency of antacid rescue. 2) Doses of 5 mg, 10 mg and 20 mg of famotidine are well-tolerated by patients with a history of heartburn, acid indigestion, or sour/upset stomach.

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV B OF THE DOSSIER TABLE 9 OF 15 REFERENCE 3 VOL 2 PAGE 20152 TO 20210	

STUDY TITLE: An Open, Three-Period, Crossover, Single-Dose, Bioavailability Study of Famotidine (MK-208) Film-Coated Tablets 10 mg, Chewable-Coated Tablets 10 mg, and Intravenous Preparation 10 mg #026

INVESTIGATOR/SITE: [redacted] Miami, FL, U.S.A.

STUDIED PERIOD: Dec. 90 | **CLINICAL PHASE:** I

DURATION: Three-period, crossover study with 24-hour treatment periods and a 72-hour washout between each period.

OBJECTIVES: To compare the pharmacokinetics of famotidine attained after the oral administration of a single dose of a 10 mg film-coated tablet vs. a single 10 mg chewable-coated tablet of famotidine. Absolute bioavailability to be estimated using the administration of a single 10 mg intravenous dose of famotidine. Due to a degradate in the chewable-coated tablet (Treatment B), samples from this treatment could not be assayed. Therefore, the bioequivalence objective could not be met.

METHODOLOGY: A single-center, open, randomized, three-period, crossover study in 18 healthy male subjects (6 groups each consisting of 35 subjects)

NUMBER OF SUBJECTS: 18, ages 19 to 44

DIAGNOSIS/INCLUSION CRITERIA: Healthy males between 18 and 45 years old and neither grossly under- nor overweight for their age and height.

DOSAGE/BATCH NOS.:

	DOSAGE FORM	STRENGTH	FORMULATION NUMBERS
Famotidine	FCT	10 mg	0208 FCT 038D001
Famotidine	CCT	10 mg	0208 OTC 022B003
Famotidine	I.V. solution	10 mg	0791S

One dose in each of the three periods.

EVALUATION CRITERIA: Plasma was assayed for famotidine at various times after each treatment. Urine samples were collected for famotidine assay; however, a validated assay to detect famotidine in urine was not available upon completion of the study.

STATISTICAL METHODS: Bioavailability and its 90% confidence interval of the 10 mg film-coated tablet (FCT) was calculated. Ratios of the AUC observed after FCT relative to that after I.V. formulation were log-transformed to calculate mean and 90% confidence interval, and those are back-transformed to get geometric mean and 90% confidence interval of bioavailability.

SUMMARY—CONCLUSIONS: 1) The absolute bioavailability of film-coated famotidine tablets is 49%. 2) The significance and etiology for the large proportion of subjects with elevated SGOT and/or SGPT values is unknown.

XPROJECT.1630/14/07DEC92

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV B OF THE DOSSIER TABLE 10 OF 15 REFERENCE 11 VOL 3 PAGE 20840 TO 20912	

STUDY TITLE: A Double-Blind, Parallel Trial to Evaluate the Efficacy and Tolerability of Famotidine 5 mg and 10 mg vs. Placebo in the Prevention of Symptoms Produced by a Test Meal #031

INVESTIGATOR/SITE: Multicenter; two investigators in the U.S.

STUDIED PERIOD: Mar. 91 to Jul. 91 | **CLINICAL PHASE:** II

DURATION: Screening test meal, then a treatment phase of two provocative meals with approximately 5-10 days between all meals.

OBJECTIVES: 1) To compare the efficacy of famotidine 5 mg and 10 mg vs. placebo in prevention of heartburn, acid indigestion or sour stomach or upset stomach, and overall discomfort produced by a test meal. 2) To compare the efficacy of famotidine 5 mg vs. famotidine 10 mg in prevention of heartburn, acid ingestion or sour stomach or upset stomach, and overall discomfort product by a test meal.

METHODOLOGY: Double-blind, parallel, placebo-controlled, randomized study

NUMBER OF SUBJECTS: Baseline Phase - A total of 748 patients entered the baseline phase. One hundred and forty-three (143) of these patients discontinued prior to randomization into the treatment phase. Four hundred and ninety-three (493) patients were randomized into the treatment phase. Ages 21 to 73.

DIAGNOSIS/INCLUSION CRITERIA: Age 21 or older with at least a 2-month history of heartburn, acid indigestion or sour/upset stomach occurring 3 times per week.

DOSAGE/BATCH NOS.:

	Dosage	Formulation Nos.
MK-208	5 mg	0208 FCT001A001
	10 mg	0208 FCT011D003
Placebo	—	P0208 FCT031A001
Maalox TC	28 mEq	83278/86890

Treatment medication taken 1 hour before test meal. Maalox TC used as a rescue medication was available for patients that developed symptoms of moderate or greater severity.

EVALUATION CRITERIA: Categorical assessment on a six-point scale for upper gastrointestinal discomfort beginning immediately before each test meal and every 15 minutes thereafter for 5 hours. Global assessment on a five-point categorical scale by the patient on how well the drug worked to be asked prior to rescue medication or at the end of each treatment session.

STATISTICAL METHODS: Global evaluations, peak heartburn, acid/sour stomach, overall discomfort, and use of rescue medication by logistic regression using SAS, PROC LOGIST. Areas under the curve (AUC) for heartburn, acid/sour stomach, and overall discomfort by parametric linear models using SAS, PROC GLM. Time to rescue medication by survival analysis using SAS, PROC PHGLM.

APPENDIX B

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV OF THE DOSSIER TABLE 10 OF 15 REFERENCE 11 VOL 3 PAGE 20840 TO 20912 Supplementary Page 2	

STATISTICAL METHODS (CONT.): All the above models included factors for treatment, period, patient, and carryover. A sample size of n=150 patients has approximately 99% power to detect a 0.6 unit difference in global evaluation score between placebo and active treatment, 88% power to detect a 0.4 unit difference in peak heartburn score, and 82% power to detect a 0.25 unit difference in heartburn AUC (at α=0.05, two tailed).

SUMMARY—CONCLUSIONS: 1) Administered 1 hour prior to a test meal, famotidine doses of 5 and 10 mg are more effective than placebo in preventing upper gastrointestinal symptoms produced by food and beverage: global evaluations are more favorable; heartburn, overall discomfort and acid/sour stomach symptoms are less severe; and antacid rescue is required less in the famotidine treated groups. 2) Famotidine 10 mg is more consistently efficacious than famotidine 5 mg. 3) Doses of 5 mg and 10 mg of famotidine are well-tolerated by patients with a history of heartburn, acid indigestion, or sour/upset stomach.

XPROJECT.1630/16/07DEC92

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV B OF THE DOSSIER TABLE 11 OF 15 REFERENCE 4 VOL 2 PAGE 20211 TO 20296	

STUDY TITLE: A Single-Dose, Three-Period, Crossover Bioavailability/Bioequivalence Study of Famotidine Film-Coated Tablets 2x5 mg, Chewable-Coated Tablets 2x5 mg, and Intravenous Preparation 10 mg #035

INVESTIGATOR/SITE: [redacted], Miami, FL, U.S.A.

STUDIED PERIOD: Nov. 91 | **CLINICAL PHASE:** I

DURATION: Each subject was monitored for plasma drug levels for 24 hours with a 5 to 7 day washout between treatments.

OBJECTIVES: To evaluate the bioequivalence of a single dose of two 5 mg film-coated tablets vs. a single dose of two 5 mg chewable-coated tablets of famotidine. Absolute bioavailability will be estimated using the administration of a single 10 mg intravenous dose of famotidine.

METHODOLOGY: Open, randomized, three-period crossover study.

NUMBER OF SUBJECTS: 15, ages 19 to 42

DIAGNOSIS/INCLUSION CRITERIA: Healthy male nonsmoking subjects between 18 and 45 years with weights not grossly above or below normal weights for their ages and heights (60 to 90 kg).

DOSAGE/BATCH NOS.:

	Dosage Form	Strength	Batch Number	Formulation Number
Famotidine	FCT	5 mg	C-X367	0208FCT043A004
Famotidine	CCT	5 mg	C-X368	0208OTC046C001
Famotidine	I.V.	10 mg/ml in 2 ml vials	C-X369	1163T

EVALUATION CRITERIA: Plasma was assayed at various times posttreatment and the following pharmacokinetic parameters were calculated for each subject: AUC $(0\text{-}\infty)$, C_{max} and T_{max}. AUC and C_{max} were the primary parameters used to measure bioequivalence for the two oral formulations. An estimate of absolute bioavailability was calculated using the ratio of AUCs observed after administration of each of the oral formulations to that observed after the administration of famotidine I.V. dose.

STATISTICAL METHODS: The sample size of 15 subjects was estimated to have 80% power (at $a = 0.05$, 2-tailed test) to detect a relative difference of 15% in AUC and 13% in C_{max} between the 2 treatments. An ANOVA model appropriate for a 3-period, 3-treatment crossover design was used to analyze AUC data. An ANOVA model appropriate for a 3-period, 2-treatment, crossover design was used to analyze C_{max} and T_{max} data. AUC data were dose-adjusted, and AUC and C_{max} data were log-transformed prior to the analysis. Ninety percent confidence intervals for the relative difference between treatments were calculated using the results of the ANOVAs. Posterior probabilities were calculated using the method of Rodda and Davis.

XPROJECT.1630/17/07DEC92

APPENDIX B

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV OF THE DOSSIER TABLE 11 OF 15 REFERENCE 4 VOL 2 PAGE 20211 TO 20296 Supplementary Page 2	

SUMMARY—CONCLUSIONS: (1) The calculated absolute bioavailability of the famotidine 5 mg FCT is 0.53 (geometric mean); (2) The famotidine 5 mg CCT and FCT formulations are bioequivalent based on the following: (a) The average AUC for the CCT is within 20% of that for the FCT. (b) The average T_{max} is similar for the 2 formulations. (c) Although the average C_{max} for the CCT may be slightly less than 80% of that for the FCT, this is unlikely to be clinically important. (3) Famotidine 10 mg administered as an I.V. solution, two 5 mg FCT and two 5 mg CCT on 3 separate occasions are generally well tolerated by healthy male subjects.

XPROJECT.1630/18/07DEC92

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV B OF THE DOSSIER TABLE 12 OF 15 REFERENCE 267 VOL 10 PAGE 24970 TO 25043	

STUDY TITLE: A Single-Dose, Open, Three-Period, Crossover Bioequivalence Study of Famotidine Film-Coated Tablets 10 mg, Chewable-Coated Tablets 10 mg, and Intravenous Preparation 10 mg #036

INVESTIGATOR/SITE: [redacted], Boston, MA U.S.A.

STUDIED PERIOD: Nov. 91 to Dec. 91 | **CLINICAL PHASE:** I

DURATION: Three panels each with one period each subject received a single dose of the three study drugs. The subjects were monitored for serum drug levels for 24 hours with at least a 5-day washout between treatments.

OBJECTIVES: To evaluate the bioequivalence of a single dose of a 10 mg film-coated tablet vs. a single 10 mg chewable-coated tablet and a single 10 mg effervescent tablet of famotidine.

METHODOLOGY: A single-center, open, randomized, three-period crossover study

NUMBER OF SUBJECTS: 15, ages 22 to 44

DIAGNOSIS/INCLUSION CRITERIA: Healthy male nonsmoking subjects between 18 and 45 years and weighing between 60 and 90 kg for his age and weight.

DOSAGE/BATCH NOS.:

Dosage	Dosage Form	Strength	Clinical Lot No.	Formulation No.
Famotidine	FCT	10 mg	C-X364	0208FCT038D002
Famotidine	CCT	10 mg	C-X365	0208OTC044B002
Famotidine	ET	10 mg	C-X366	0208EFT012B001

EVALUATION CRITERIA: Plasma was assayed for famotidine levels at various times posttreatment and following pharmacokinetic parameters were calculated for each subject: AUC $(0-\infty)$ and C_{max} to evaluate bioequivalence for the chewable-coated and effervescent tablets compared to the film-coated tablet. Routine hematology chemistry, and urinalysis was performed pre and 24 hours post Period 3 for safety assessment.

STATISTICAL METHODS: The sample size of n = 15 has 80% power to detect (at a = 0.05, two-tailed test) a difference of 15% in AUC and 13% in C_{max} between each two treatments (17% in AUC and 16% in C_{max} with 90% power).

An ANOVA model appropriate for a 3-period, 3-treatment, crossover design was used to analyze AUC, C_{max}, and T_{max} data. AUC data were dose-adjusted, and AUC and C_{max} data were log-transformed prior to the analysis. Ninety percent confidence intervals for the relative difference between treatments were calculated using the results of the ANOVAs. Posterior probabilities were calculated using the method of Rodda and Davis.

SUMMARY—CONCLUSIONS: (1) The 10 mg famotidine effervescent tablet and 10 mg famotidine film-coated tablet are bioequivalent, as measured by AUC and C_{max}; (2) The 10 mg chewable-coated tablet and 10 mg film-coated tablet are bioequivalent, as measured by AUC and C_{max}; (3) T_{max} for the chewable-coated tablet and effervescent tablet are similar to the T_{max} for the film-coated tablet, and (4) Famotidine administered as one 10 mg film-coated tablet, one 10 mg coated-chewable tablet, and one 10 mg effervescent tablet on 3 separate occasions is well tolerated by healthy male subjects.

APPENDIX B

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV B OF THE DOSSIER TABLE 13 OF 15 REFERENCE 12 VOL 3 PAGE 20913 TO 20947	

STUDY TITLE: A Single-Blind, Taste Test to Evaluate Three Flavors of ZYDIS Tablets Containing 10 mg of Famotidine #039

INVESTIGATOR/SITE: [redacted] four centers in the U.S.

STUDIED PERIOD: Dec. 91 | **CLINICAL PHASE:** II

DURATION: Screening phone call, treatment period of two tablets taken approximately 15 minutes apart with a 24-hour follow-up phone call.

OBJECTIVES: 1) To determine whether 10 mg of famotidine in the ZYDIS formulation is acceptable for general marketing. 2) To determine which of the three flavors (peppermint, peppermint-caramel or peppermint-banana) is preferred by consumers.

METHODOLOGY: Single-blind, balanced incomplete block study

NUMBER OF SUBJECTS: 540, ages 23 to 66

DIAGNOSIS/INCLUSION CRITERIA: Age 25 to 65 (60% female, 40% male) and must have used an antacid product in the past 3 months for treatment of upper G.I. disorders.

DOSAGE/BATCH NOS.:	Dosage	Formulation Nos.
MK-208 Peppermint	10 mg	02080LL014C002
MK-208 Peppermint/Caramel	10 mg	02080LL020C001
MK-208 Peppermint/Banana	10 mg	02080LL019C001

Treatment medication #1 was taken upon completion of questionnaire, after approximately 15 minutes, treatment #2 was taken.

EVALUATION CRITERIA: Subjects answered a series of marketing research questions regarding purchase intent, overall rating, likes/dislikes and certain attribute ratings about the product they tested. Subjects were monitored for adverse experiences during the taste test and received a telephone contact 24 hours after the taste test as a follow-up for safety information.

STATISTICAL METHODS: Bruno and Ridgeway Research Associates, Inc., was responsible for the marketing analysis of product preference. Johnson & Johnson•Merck was responsible for monitoring safety results.

SUMMARY—CONCLUSIONS: Famotidine ZYDIS 10 mg tablets were well-tolerated by volunteer subjects who took a total of two tablets approximately 15 minutes apart.

XPROJECT.1630/20/07DEC92

APPENDIX B

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV B OF THE DOSSIER TABLE 14 OF 15 REFERENCE 13 VOL 3 PAGE 20948 TO 20978	

STUDY TITLE: A Single-Blind, Taste Test to Determine Acceptability of 5 mg and 10 mg of Famotidine in the Mint ZYDIS Formulation #040

INVESTIGATOR/SITE: [redacted], 4 centers in the U.S.

STUDIED PERIOD: Dec. 91 | **CLINICAL PHASE:** II

DURATION: Screening phone call, treatment period of two tablets taken approximately 15 minutes apart with a 24-hour follow-up phone call.

OBJECTIVES: 1) To determine whether 5 mg and 10 mg of famotidine in the ZYDIS formulation are equally acceptable for general marketing. 2) To determine if differences exist between the 5 mg and 10 mg strengths of famotidine in the ZYDIS formulation, in terms of taste acceptance.

METHODOLOGY: Single-blind, balanced, incomplete block study

NUMBER OF SUBJECTS: 360, ages 25 to 66

DIAGNOSIS/INCLUSION CRITERIA: Age 25 to 65 (60% female, 40% male) and must have used an antacid product in the past 3 months for treatment of upper G.I. disorders.

DOSAGE/BATCH NOS.:	Dosage	Formulation Nos.
MK-208 Peppermint	5 mg	02080LL013E002
MK-208 Peppermint	10 mg	02080LL014C002

EVALUATION CRITERIA: Subjects answered a series of marketing research questions regarding purchase intent, overall rating, likes/dislikes and certain attribute ratings about the product they tested. Subjects were monitored for adverse experiences during the taste test and received a telephone contact 24 hours after the taste test as a follow-up for safety information.

STATISTICAL METHODS: Bruno and Ridgeway Research Associates, Inc., was responsible for the marketing analysis of product preference. Johnson & Johnson/Merck was responsible for monitoring safety results.

SUMMARY—CONCLUSIONS: Famotidine ZYDIS 5 mg and 10 mg tablets were well-tolerated by volunteer subjects who took a total of two tablets (15 mg total) approximately 15 minutes apart.

MERCK RESEARCH LABS FAMOTIDINE TABLETS FAMOTIDINE OTC (MK-208)	TABULAR SUMMARIZATION REFERRING TO PART IV B OF THE DOSSIER TABLE 15 OF 15 REFERENCE 268 VOL 10 PAGE 25044 TO 25073	

STUDY TITLE: A Single-Blind, Open, Two-Period, Crossover Bioequivalence Study of Famotidine, Film-Coated Tablets 10 mg and Famotidine ZYDIS Wafers, 10 mg #044

INVESTIGATOR/SITE: [redacted], Austin, TX U.S.A.

STUDIED PERIOD: Mar. 92 | **CLINICAL PHASE:** I

DURATION: Two panels each with one-period. Each subject received a single dose of the two study drugs. The subjects were monitored for serum drug levels for 24 hours with at least a 5-day washout between treatments.

OBJECTIVES: To evaluate the bioequivalence of a single dose of 10 mg film-coated tablets vs. a single dose of 10 mg ZYDIS wafer of famotidine.

METHODOLOGY: A single-center, open, 2-period, randomized crossover study

NUMBER OF SUBJECTS: 18, ages 18 to 40

DIAGNOSIS/INCLUSION CRITERIA: Healthy male subjects between 18 and 45 years and weighing between 60 and 90 kg for age and height.

DOSAGE/BATCH NOS.:

Dosage	Dosage Form	Strength	Clinical Lot No.	Formulation No.
Famotidine	Film-coated tablet	10 mg	C-X718	0208FCT038D001
Famotidine	ZYDIS wafer	10 mg	C-X719	02080LL022C001

EVALUATION CRITERIA: Plasma was assayed for famotidine levels at various time posttreatment. Routine hematology, chemistry, and urinalysis was performed pre and 24 hours post Period 2 for safety assessment.

STATISTICAL METHODS: This will be completed when pharmacokinetic results are available.

SUMMARY—CONCLUSIONS: Famotidine 10 mg administered orally as one film-coated tablet and one ZYDIS wafer on two separate occasions is well tolerated by healthy male subjects.

ZYDIS STUDY #041 IS IN SEPARATE DOCUMENT - XPROJECT.1964

TABLE 12

Overall Patterns of Adverse Responses During OTC Studies [24]

Body System	Famotidine	Antacid	Placebo
Body as a Whole/ Site unspecified	2.7 (0.6)	3.1 (0)	1.9 (0.6)
Cardiovascular	0.3 (<0.1)	1.6 (0)	0.2 (0)
Digestive	5.4 (2.4)	6.6 (1.2)	4.2 (2.1)
Diarrhoea	1.4 (0.5)	1.6 (0.4)	0.7 (0.2)
Nausea	1.4 (0.7)	1.9 (0.4)	1.2 (0.8)
Nervous	11.1 (4.0)	8.9 (0.8)	13.2 (5.3)
Dizziness	1.5 (1.1)	0.8 (0)	1.9 (1.6)
Headache	9.8 (3.3)	7.0 (0.4)	11.9 (4.1)
Respiratory	3.3 (0.1)	9.3 (0)	4.1 (0.2)
Upper resp. infection	1.3 (0)	3.1 (0)	1.3 (0)
Musculoskeletal	1.7 (<0.1)	3.5 (0.4)	2.7 (0)
Skin	0.8 (<0.1)	1.6 (0)	1.2 (0.4)
Special Senses	0.6 (0.3)	1.6 (0)	0.6 (0.1)
Urogenital	0.8 (<0.1)	0.8 (0)	1.1 (0)
Blood	0 (0)	0.4 (0.4)	0.1 (0.1)
	2350	257	857

(Figures in brackets denote responses considered treatment related.)

Table B11 Percentage of Patients/Subjects in Each Treatment Group With Clinical Adverse Experiences Occurring in More Than 1 Patient and <1% of the Total Famotidine-Treated Population in Investigational Studies for OTC Indications* [17]

Clinical Adverse Experience by Body System	Famotidine$^{\Delta}$ (n=2350)	Antacid (n=257)	Placebo (n=857)
Body as a Whole			
Abdominal Pain	0.9 (0.3)	0.8 (0)	1.1 (0.5)
Asthenia	0.3 (0.1)	0.4 (0)	0
Chest Pain	0.3 (0)	0	0.1 (0)
Chills	0.1 (0.1)	0	0.1 (0.1)
Edema	0.1 (0)	0.8 (0)	0.4 (0)
Fever	0.3 (0)	0.4 (0)	0.1 (0)
Flu-Like Illness	0.3 (0)	0.8 (0)	0.1 (0)
Malaise	0.1 (<0.1)	0	0
Pain	0.1 (0)	0	0
Pelvic Pain	0.1 (0)	0	0
Syncope	0.1 (0.1)	0	0
Trauma	0.1 (0)	0.4 (0)	0.1 (0)
Virus Infection	0.1 (0)	0	0
Cardiovascular System			
Tachycardia, NOS	0.1 (<0.1)	0	0
Digestive System			
Acid Regurgitation	0.3 (0.1)	0	0
Constipation	0.7 (0.4)	0	0.7 (0.4)
Dental Pain	0.1 (0)	0	0
Dry Mouth	0.3 (0.3)	0.4 (0.4)	0.1 (0.1)
Dyspepsia	0.3 (0.1)	0	0
Esophagitis	0.1 (0)	0	0.4 (0.1)
Flatulence	0.3 (0.2)	1.2 (0.4)	0.5 (0.2)
Gastric Ulcer	0.2 (0)	0.8 (0)	0.1 (0)
Mouth Pain	0.1 (0)	0	0
Reflux Esophagitis	0.1 (<0.1)	0	0.1 (0.1)
Vomiting	0.7 (0.3)	1.9 (0.4)	0.6 (0.4)

* Percentage of patients with clinical adverse experiences judged by the investigator to be possibly, probably or definitely related to the test drug are shown in parentheses.

$^{\Delta}$ In one study, subjects received famotidine and antacid administered together. They are counted in the famotidine group.

NOS = Not Otherwise Specified

Table B11 (Cont.) Percentage of Patients/Subjects in Each Treatment Group With Clinical Adverse Experiences Occurring in More Than 1 Patient and <1% of the Total Famotidine-Treated Population in Investigational Studies for OTC Indications* [17]

Clinical Adverse Experience by Body System	Famotidine$^{\Delta}$ (n=2350)	Antacid (n=257)	Placebo (n=857)
Musculoskeletal System			
Arthritis, NOS	0.1 (0)	0	0.2 (0)
Back Pain	0.4 (0)	0.4 (0)	0.4 (0)
Knee Pain	0.1 (0)	0	0.1 (0)
Leg Pain	0.1 (0)	0	0
Low Back Pain	0.1 (<0.1)	0	0
Musculoskeletal Pain	0.1 (0)	0.8 (0)	0.5 (0)
Myalgia	0.2 (0)	0.8 (0)	0.4 (0)
Neck Stiffness	0.1 (0)	0.4 (0)	0
Shoulder Pain	0.1 (0)	0.4 (0)	0.2 (0)
Sprains & Strains	0.1 (0)	0	0.1 (0)
Nervous System and Psychiatric			
Anxiety Disorders	0.1 (0.1)	0	0
Insomnia	0.2 (0)	0	0
Migraine	0.1 (0)	0.4 (0.4)	0
Paresthesia	0.1 (0.1)	0	0
Somnolence	0.2 (0.2)	0	0.6 (0.6)
Respiratory System			
Bronchitis	0.1 (0)	0.8 (0)	0.1 (0)
Cough	0.2 (0)	1.2 (0)	0.4 (0)
Influenza	0.3 (0)	0.4 (0)	0.1 (0)
Pharyngitis	0.7 (0)	2.3 (0)	0.4 (0)
Rhinitis	0.1 (<0.1)	0	0.2 (0.1)
Rhinorrhea	0.3 (0)	0.4 (0)	0.4 (0.1)
Sinusitis	0.6 (<0.1)	1.6 (0)	0.8 (0)
Skin and Skin Appendage			
Contusion	0.1 (0)	0	0.1 (0)
Flushing	0.1 (<0.1)	0	0
Rash	0.2 (0)	0.8 (0)	0.4 (0.2)
Skin Infections	0.1 (0)	0	0.2 (0)

* Percentage of patients with clinical adverse experiences judged by the investigator to be possibly, probably or definitely related to the test drug are shown in parentheses.

$^{\Delta}$ In one study, subjects received famotidine and antacid administered together. They are counted in the famotidine group.

NOS = Not Otherwise Specified

Table B11 (Cont.) Percentage of Patients/Subjects in Each Treatment Group With Clinical Adverse Experiences Occurring in More Than 1 Patient and <1% of the Total Famotidine-Treated Population in Investigational Studies for OTC Indications* [17]

Clinical Adverse Experience by Body System	Famotidine$^{\Delta}$ (n=2350)	Antacid (n=257)	Placebo (n=857)
Special Senses			
Blurred Vision	0.1 (0.1)	0	0.1 (0.1)
Ear Pain	0.1 (0)	0.4 (0)	0
Taste Perversion	0.1 (0.1)	0	0
Urogenital System			
Breast Mass	0.1 (0)	0	0
Dysmenorrhea	0.3 (0)	0	0.5 (0)
Dysuria	0.1 (0)	0	0
Urinary Frequency	0.1 (<0.1)	0	0

* Percentage of patients with clinical adverse experiences judged by the investigator to be possibly, probably or definitely related to the test drug are shown in parentheses.

$^{\Delta}$ In one study, subjects received famotidine and antacid administered together. They are counted in the famotidine group.

Table B12 Number and Percentage of Patients/Subjects by Famotidine Dose With at Least One Clinical Adverse Experience in Investigational Studies for OTC Indications [17]

Famotidine Dose (mg)	Total No. of Patients/ Subjects*	No. of Patients/ Subjects with at Least One Clinical AE	Percent of Patients/ Subjects with Clinical AEs	Percent of Patients/ Subjects with Drug-Related Clinical AE**
0.5	10	1	10.0	10.0
2.5	10	0	0	0
5.0	708	167	23.6	7.6
10.0	926	192	20.7	6.4
15.0	360	20	5.6	1.9
20.0	1225	144	11.8	1.9
TOTAL	3239			

* These counts include patients in crossover trials who are counted once for each different famotidine dose they received.

** Clinical adverse experiences judged by the investigator to be possibly, probably or definitely related to famotidine therapy.

Table B13 Percentage of Patients/Subjects By Famotidine Dose With Any Clinical Adverse Experience by Body System in Investigational Studies for OTC Indications* [17]

Clinical Adverse Experience by Body System	Famotidine Dose 0.5 mg (n=10)	2.5 mg (n=10)	5 mg (n=708)	10 mg (n=926)	15 mg (n=360)	20 mg (n=1225)
Body as a Whole/ Site Unspecified	0	0	1.7 (0.3)	2.9 (0.9)	1.4 (0.3)	1.6 (0.2)
Cardiovascular System	0	0	0.3 (0)	0.1 (0.1)	0	0.2 (0)
Digestive System	10.0 (10.0)	0	4.9 (2.1)	4.2 (1.8)	2.8 (1.1)	3.7 (1.6)
Metabolic/Nutritional/ Immune System	0	0	0.1 (0)	0	0	0
Musculoskeletal System	0	0	1.4 (0)	2.1 (0)	0	1.1 (0.1)
Nervous System and Psychiatric	0	0	15.4 (6.2)	12.0 (4.9)	1.7 (0.3)	4.3 (0.3)
Respiratory System	0	0	2.8 (0.1)	3.6 (0.2)	0.3 (0)	2.1 (0)
Skin/Skin Appendage	0	0	0.4 (0.1)	0.8 (0)	0	0.7 (0)
Special Senses	0	0	0.3 (0.3)	0.8 (0.4)	0.3 (0.3)	0.2 (0.1)
Urogenital System	0	0	0.4 (0)	0.8 (0)	0	0.7 (0.1)

* Percentage of patients with clinical adverse experiences judged by the investigator to be possibly, probably or definitely related to famotidine therapy are shown in parentheses.

Table B14 Percentage of Patients/Subjects by Famotidine Dose With Clinical Adverse Experiences Occurring in ≥1% of Patients/Subjects in Investigational Studies for OTC Indications* [17]

Clinical Adverse Experience by Body System	Famotidine Dose					
	0.5 mg (n=10)	2.5 mg (n=10)	5 mg (n=708)	10 mg (n=926)	15 mg (n=360)	20 mg (n=1225)
Body as a Whole/ Site Unspecified						
Abdominal Pain	0	0	0.6 (0)	1.1 (0.4)	1.1 (0.3)	0.3 (0.2)
Digestive System						
Diarrhea	0	0	1.1 (0.1)	1.4 (0.6)	0	1.1 (0.3)
Nausea	10.0 (10.0)	0	1.0 (0.6)	1.0 (0.4)	1.1 (0.6)	1.0 (0.6)
Vomiting	0	0	1.0 (0.6)	0.2 (0)	0	0.7 (0.3)
Nervous System/ Psychiatric						
Dizziness	0	0	2.3 (1.8)	1.7 (1.3)	0	0.2 (0.1)
Headache	0	0	14.0 (4.9)	10.6 (4.1)	1.7 (0.3)	3.8 (0.2)
Respiratory System						
Pharyngitis	0	0	0.3 (0)	1.0 (0)	0	0.4 (0)
Upper Respiratory Infection, NOS	0	0	1.3 (0)	1.3 (0)	0	0.9 (0)

* Percentage of patients with clinical adverse experiences judged by the investigator to be possibly, probably or definitely related to famotidine therapy are shown in parentheses.
NOS = Not Otherwise Specified

MSD

Table B15 Percentage of Patients/Subjects by Famotidine Dose With Clinical Adverse Experiences Occurring in More Than 1 Patient/Subject and <1% of Patients/Subjects in Investigational Studies for OTC Indications* [17]

Clinical Adverse Experience by Body System	Famotidine Dose 0.5 mg (n=10)	2.5 mg (n=10)	5 mg (n=708)	10 mg (n=926)	15 mg (n=360)	20 mg (n=1225)
Body as a Whole						
Asthenia	0	0	0	0.4 (0.2)	0	0.2 (0)
Chest Pain	0	0	0.1 (0)	0.3 (0)	0	0.2 (0)
Chills	0	0	0.1 (0.1)	0.2 (0.1)	0	0
Fever	0	0	0.1 (0)	0.3 (0)	0	0.2 (0)
Flu-Like Illness	0	0	0.3 (0)	0	0	0.3 (0)
Pain	0	0	0	0	0	0.2 (0)
Syncope	0	0	0	0.2 (0.2)	0	0
Trauma	0	0	0	0.2 (0)	0	0
Digestive System						
Acid Regurgitation	0	0	0.1 (0)	0	0.8 (0)	0.3 (0.2)
Constipation	0	0	0.6 (0.3)	0.6 (0.3)	0.3 (0.3)	0.4 (0.3)
Dry Mouth	0	0	0.6 (0.6)	0.4 (0.3)	0	0
Dyspepsia	0	0	0.4 (0.3)	0.1 (0)	0	0.2 (0)
Flatulence	0	0	0	0.2 (0.1)	0.3 (0.3)	0.2 (0.2)
Gastric Ulcer	0	0	0.3 (0)	0.2 (0)	0	0
Reflux Esophagitis	0	0	0.3 (0.1)	0	0	0.1 (0)
Musculoskeletal System						
Back Pain	0	0	0.7 (0)	0.3 (0)	0	0.2 (0)
Leg Pain	0	0	0	0.2 (0)	0	0
Low Back Pain	0	0	0	0.1 (0)	0	0.2 (0.1)
Musculoskeletal Pain	0	0	0	0.2 (0)	0	0
Myalgia	0	0	0	0.2 (0)	0	0.2 (0)
Shoulder Pain	0	0	0	0	0	0.2 (0)
Nervous System and Psychiatric						
Anxiety Disorders	0	0	0.1 (0.1)	0	0	0.2 (0.1)
Insomnia	0	0	0.3 (0)	0.2 (0)	0	0
Paresthesia	0	0	0	0.2 (0.2)	0	0
Somnolence	0	0	0.3 (0.3)	0.3 (0.3)	0	0

* Percentage of patients with clinical adverse experiences judged by the investigator to be possibly, probably or definitely related to famotidine therapy are shown in parentheses.

Table 815 (Cont.) Percentage of Patients/Subjects by Famotidine Dose With Clinical Adverse Experiences Occurring in More Than 1 Patient/Subject and <1% of Patients/Subjects in Investigational Studies for OTC Indications* [17]

Clinical Adverse Experience by Body System	Famotidine Dose 0.5 mg (n=10)	2.5 mg (n=10)	5 mg (n=708)	10 mg (n=926)	15 mg (n=360)	20 mg (n=1225)
Respiratory System						
Bronchitis	0	0	0	0	0	0.2 (0)
Cough	0	0	0.1 (0)	0.2 (0)	0	0.1 (0)
Influenza	0	0	0.3 (0)	0.3 (0)	0	0.2 (0)
Rhinitis	0	0	0.3 (0.1)	0	0	0
Rhinorrhea	0	0	0.1 (0)	0.4 (0)	0	0.2 (0)
Sinusitis	0	0	0.4 (0)	0.6 (0.1)	0	0.3 (0)
Skin and Skin Appendage						
Contusion	0	0	0.1 (0)	0.2 (0)	0	0
Rash	0	0	0	0.1 (0)	0	0.2 (0)
Skin Infections	0	0	0	0	0	0.2 (0)
Special Senses						
Taste Perversion	0	0	0.1 (0.1)	0.2 (0.2)	0	0
Urogenital System						
Breast Mass	0	0	0	0	0	0.2 (0)
Dysmenorrhea	0	0	0.3 (0)	0.3 (0)	0	0.1 (0)
Urinary Frequency	0	0	0	0	0	0.2 (0.1)

* Percentage of patients with clinical adverse experiences judged by the investigator to be possibly, probably or definitely related to famotidine therapy are shown in parentheses.

[redacted]

Table B16

Nonfatal Serious Clinical Adverse Experiences Report (OTC Environment: Investigational Studies
Indications) [18]

Investigator/Country	Study/ Allgc. No.	WAES No.	Age/ Sex	Daily Dose* (mg)	Study Day	Adverse Experience	Drug Relation	Comments
Body as a Whole								
1. [redacted] UNITED STATES	[redacted]			10	[redacted]	CHEST PAIN	PROB NOT	[redacted]
2. [redacted] UNITED STATES				5/ PRN		TACHYCARDIA CORONARY ATHEROSCLEROSIS	DEF NOT DEF NOT	

N/R = Not Reported
* = This represents the daily dose of famotidine the patient was assigned to receive during the study.

Table B31 Number and Percent of Famotidine-Treated Patients With at Least One Clinical Adverse Experience Within Each Age Range in Investigational Studies for OTC Indications [17]

Age Range	Total Number of Patients	Number of Patients With at Least One Clinical Adverse Experience	Percent of Patients With Clinical Adverse Experience	Percent of Patients With Drug Related Adverse Experiences*
<65	2,146	447	20.8	6.0
65 to 75	98	21	21.4	4.1
>75	10	3	30.0	0

* Clinical adverse events considered possibly, probably or definitely drug related by the investigator.

Table B32 Percentage of Famotidine-Treated Patients With Clinical Adverse Experiences Within Each Body System with Respect to Age in Investigational Studies for OTC Indications* [17]

Clinical Adverse Experience By Body System	<65 Years (n=2146)	65-75 Years (n=98)	>75 Years (n=10)
Body as a Whole/Site Unspecified	2.6 (0.4)	2.0 (1.0)	0
Cardiovascular System	0.3 (0)	0	0
Digestive System	5.4 (2.4)	7.1 (3.1)	10.0 (0)
Metabolic/Nutritional/Immune System	<0.1 (0)	0	0
Musculoskeletal System	1.7 (0)	3.1 (1.0)	10.0 (0)
Nervous System/Psychiatric	11.3 (4.0)	9.2 (1.0)	10.0 (0)
Respiratory System	3.5 (0.1)	3.1 (0)	0
Skin and Skin Appendage	0.7 (<0.1)	3.1 (0)	0
Special Senses	0.6 (0.4)	0	0
Urogenital	0.8 (<0.1)	2.0 (0)	0

* Percent of patients with clinical adverse experiences judged by the investigator to be possibly, probably or definitely related to the test drug are shown in parentheses.

1) Clinical Adverse Experiences in Elderly Patients (Investigational Studies for OTC Indications) (Cont.)

Individual adverse events occurring in ≥1% and in more than one patient in the famotidine-treated population with respect to age are shown in Table B33.

Table B33 Percentage of Famotidine-Treated Patients With Clinical Adverse Experiences Occurring in ≥1% of Patients and More Than One Patient by Age Range in Investigational Studies for OTC Indications* [17]

Clinical Adverse Experience by Body System	<65 Years (n=2146)	65-75 Years (n=98)	>75 Years (n=10)
Digestive System			
Constipation	0.6 (0.3)	3.1 (3.1)	0
Diarrhea	1.4 (0.5)	1.0 (0)	10.0 (0)
Dyspepsia	0.1 (0.1)	3.1 (0)	0
Nausea	1.3 (0.7)	1.0 (1.0)	0
Nervous System/Psychiatric			
Dizziness	1.5 (1.2)	2.0 (0)	0
Headache	10.1 (3.3)	7.1 (1.0)	10.0 (0)
Respiratory System			
Upper Resp. Infection, NOS	1.4 (0)	2.0 (0)	0

* Percent of patients with clinical adverse experiences judged by the investigator to be possibly, probably or definitely related to test drug are shown in parentheses.

NOS = Not Otherwise Specified

1. Problem Statement

An O.T.C. acid suppressant needs to have the following properties:

A. It reduces gastric acid output at the dose proposed.

B. There is associated symptom relief.

C. Drug safety is assured.

D. Serious disease is not masked by self-medication.

2. Clinical Pharmacology

2.1. Pharmacodynamics

2.1.1. Effects on Gastric Acid Secretion

Famotidine differs little in properties from cimetidine, ranitidine, and nizatidine, all of which are marketed currently in the United Kingdom. It is a competitive reversible inhibitor of histamine H_2 receptors. The accepted standard doses are of 20 to 40 mg in peptic ulcer disease or gastroesophageal reflux, which equate to doses of 400 to 800 mg of cimetidine, or 150 to 300 mg of ranitidine.

2.1.1.1. Dose-Ranging Studies

Doses of famotidine for use in treating peptic ulcer or reflux have been justified in the past by pharmacodynamic and also pharmacokinetic studies as well as by trials to examine efficacy. However use in treating digestive symptoms in an over-the-counter remedy necessitates dose-ranging pharmacodynamic studies conducted under the likely conditions of ordinary use.

Over-the-counter doses are certainly unlikely to be greater than standard prescribed doses, and might be expected to be lower. A range of doses from 0.5 mg to 10 mg has been tested against between meal and meal stimulated acidity using an intragastric pH probe and analysing continuous intragastric pH traces [1].

Ten male volunteers were studied according to a crossover design and results can be summarised as follows:

(a) In the period up to 3 hours after dosing there was a progressive increase in effect as doses rose.

(b) Only doses of 5 or 10 mg maintained pH at or above pH 2 in that period.

(c) From 3 to 5½ hours after dosing mean pH was consistently raised after the 10 mg dose, reaching a figure at or about 4.0, but did not differ materially for doses below that from placebo figures. They are best illustrated graphically to show the timing of meals, medication and pH traces (Figure 1).

Dose-dependent variation in patterns of secretory inhibition have in the past been detected by other conventional tests [2]. Thus, mean percentage inhibition of acid output in response to pentagastrin at 45 to 105 minutes after dosing with famotidine 5, 10 and 20 mg doses was respectively 63.0, 72.5 and 91.3%. A second study [3] showed a similar trend with 50, 69 and 87% inhibition, respectively.

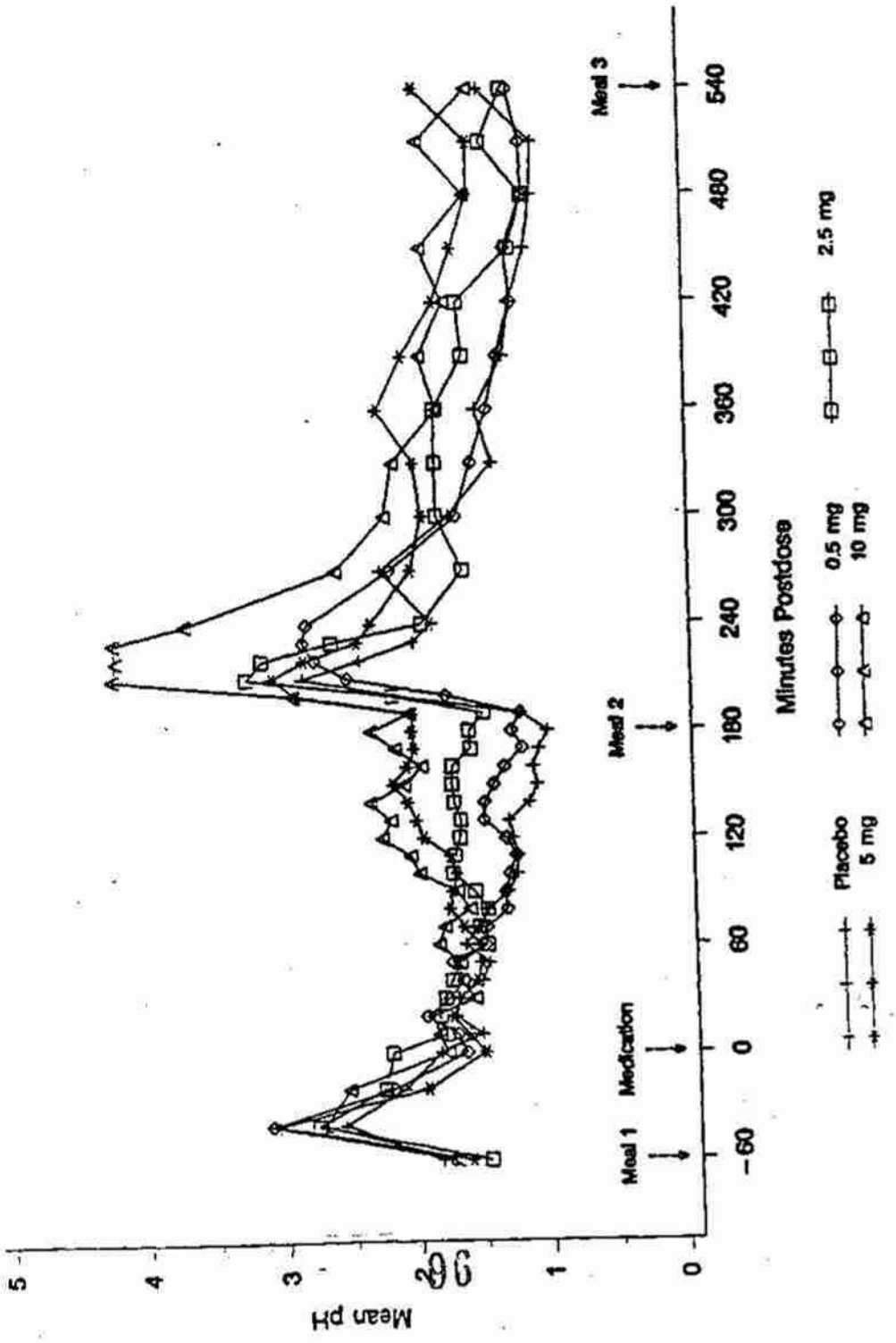
Choice of a dose is somewhat arbitrary, but Figure 1 suggests that mean pH tended to be raised to a greater extent and for a period up to 5½ hours after dosing with the

10 mg dose, whilst the 5 mg dose showed some but a lesser effect up to 3 hours and little or no effect thereafter.

A 10 mg dose seems from this evidence a sensible dose to consider for further studies.

FIGURE 1

Mean Intragastric pH Response Before and Following Famotidine
[-60 Minutes (-1 Hour) to 540 Minutes (9 Hours)] [1]



2.1.1.2. Coadministration of Antacid

Coadministration of a magnesium-aluminum antacid containing simethicone, and which had a neutralising capacity of 50 mEq (a standard moderate to high potency antacid) had no effect on the acid suppressant activity of famotidine, in doses of 10 or 20 mg [4]. Intragastric acidity was measured with a pH probe and drugs were administered 1 hour after a standardized meal. Acidity was greatest, as might be expected, after dummy antacid and dummy famotidine treatment. The greatest rise in pH in the first 4 hours was after 10 mg of famotidine and a single antacid tablet. Thereafter pH was greatest after the 10 mg dose with a two-tablet antacid dose. However, patterns were rather inconsistent and there was no evidence that coadministration of antacid dose dependently interfered with famotidine effects.

2.1.2. Other Effects - Receptor Selectivity

Famotidine is inactive at muscarinic, nicotinic, histamine H_1 and sympathetic α and ß receptors [9]. Histamine H_2 receptors are fairly widely distributed outside the stomach. Intravenous administration of famotidine had little or no effect upon changes of blood pressure or heart rate induced by histamine, adrenaline, acetyl choline or vagal stimulation [24].

In man, there have been demonstrable effects of H_2 antagonists, usually cimetidine when given intravenously in altering heart rate, in inducing prolactin secretion, in competitively displacing dihydrotestosterone from androgen binding sites in modulating immune function and in retarding hepatic metabolism of drugs by cytochrome P450 [24].

2.1.2.1. Cardiovascular Effects

No consistent effects on cardiac function were demonstrable [24]. Variations within but not outside the physiological range were observed with intravenous dosing of 20 mg twice daily [5,6,7,8].

2.1.2.1.1. Antiandrogenic Effects

No displacement from androgen-binding sites has been observed [24].

2.1.2.1.2. Immune Function

Mast cell mediator release has not been observed [10,11].

2.1.2.1.3. Hepatic Drug Metabolism

Mixed function oxidase activity is unaffected [9,12].

2.2. Pharmacokinetics

Useful confirmation of likely lack of interference with antisecretory power by concurrent antacid administration would derive from any studies which showed blood levels of drug to be unaffected. Measurement of the area under the curve (AUC) of famotidine plasma concentrations (using log-transformed data) showed figures of 490.5 ng·hr/ml (157.2 S.D), 528.1 (141.6) and 452.8 (136.1) for the 10 mg dose with respectively no, one and two tablets of antacid, each of 23 mEq neutralising capacity. Since the study was conducted in 9 subjects it lacks power, standard errors being circa 50 ng·hr/ml. However, very similar figures were attained using 20 mg when dose adjusted AUC data were calculated [4].

The results showed that if anything, mean AUC levels were higher with one antacid tablet given concurrently, and about 10% lower when two antacid tablets were given concurrently. The lack of a clear antacid dose-dependent reduction in blood levels, the small size of any mean change at the highest dose, and the overall uniformity of the data suggest that there are unlikely to be material effects of concurrent antacid intake upon drug absorption.

Peak plasma concentrations are usually attained 1 to 3½ hours after oral dosing, with an elimination half-life of 2½ to 4 hours. Drug is substantially eliminated after 12 hours and completely by 24 hours. Approximately one fifth of drug taken is plasma protein bound. Renal clearance is high with evidence supporting tubular secretion of drug, major proportions being as free drug or its sulphoxide [9,12].

Drug elimination is, as would be expected, slowed in those with moderately to severely impaired renal function. The elimination half-life of patients with renal clearances of less than 10 ml per minute per 1.48 m^2 was 13 hours [14,15,16].

3. Review of Clinical Efficacy

A constellation of symptoms needs to be identified by the potential taker as suitable for treatment and that remedy then needs to be shown to alleviate those symptoms.

Visceral pain tends to be ill-defined, and this makes it difficult to characterize indications for individual treatments which can be clearly recognized. Some symptoms tend to be associated in the public mind with acid exposure leading to phrases such as acid indigestion, whereas others, such as abdominal distension seem less likely to be caused by acid. Since scientific rationale for common behaviour is lacking the design of trials is difficult.

In the present case the company has chosen heartburn as their target symptom. This has merits and problems. On the one hand heartburn tends to be linked generally with the consequences of acid exposure, and hence its effects should be suppressed by acid secretory suppression or neutralization, on the other hand pain may derive from other visceral areas, and over acidity may result in other symptoms, which, however ill defined, could respond to measures modulating acidity.

For present purposes it is enough to decide whether the drug actually affects perceived symptoms, it being axiomatic that if individuals can choose whether to self medicate and if after their choice the treatment is effective then efficacy for that indication is demonstrated.

Two studies [17,18] have been performed in which individuals who had self medicated in the past for heartburn with antacids were; in the first; randomly

assigned to receive placebo antacid or famotidine in doses of 5, 10 or 20 mg daily, and in a second study to receive placebo, antacid and 10 or 20 mg of famotidine.

3.1. Study 1 [17]

3.1.1. Design of Study

Individuals self medicating for heartburn were enrolled having given consent to initial endoscopic, manometric and motility study before random allocation to placebo, antacid [11 mEq neutralising capacity] or famotidine 5, 10, 20 mg daily. All preparations were given in blister packs and were apparently identical. Treatment was preceded by a week's run-in during which patients had to develop at least three attacks of heartburn for which they took antacids (though not necessarily achieving complete relief).

Patients were told to take one dose of test treatment when an episode of heartburn occurred. If symptoms were not relieved within an hour, they were permitted to take a single dose of additional antacid (of 11 mEq neutralising capacity). If symptoms had not remitted in 3 hours, a second dose of test medication was permitted. All self treatment and symptomatic responses were recorded on diary cards.

3.1.2. Study Results

Those receiving each treatment were well matched for endoscopic diagnoses, manometric features, and for age, sex, smoking and drinking habits (Tables 1 and 2). Distinct oesophageal abnormalities were quite commonly detected with approximately 40% of individuals in all groups having evidence of haemorrhagic oesophagitis, erosions or overt ulcer (grades 2-4) and a further 4 to 9% had overt gastroduodenal ulcer. Numbers of ulcers were highest in antacid recipients, but were still too few to be likely to have skewed symptomatic assessment.

3.1.3. Efficacy Results

Five hundred and sixty-five individuals were assigned treatment. Global efficacy data were obtained in 475 (84%) and other individual measures, % of episodes relieved, % of episodes requiring back-up antacid, % of episodes requiring re-medication, time to relieve first episodes and number of episodes were studied in 491 subjects (Table 3).

3.1.3.1. Global Evaluation

Good or excellent results were obtained in 60% of placebo and 69% of antacid recipients and in 69, 74 and 75% respectively of recipients of 5, 10 and 20 mg of famotidine, all differences being statistically significant except for antacid. Similar trends were seen for other measures with more individuals with episodes relieved after famotidine use, particularly in doses of 10 or 20 mg, but also and to a lesser extent after both antacid and 5 mg of famotidine compared with placebo, and less episodes requiring back-up antacid. Little difference was seen in number of episodes requiring self medication (although placebo recipients fared worse) or in time to relief of first episode, and the mean number of episodes did not differ statistically according to treatment received.

The measures employed are, with the exception of the number of episodes, linked to each other and there is some uniformity in indicating that treatment either antacid or famotidine is better than placebo, and that with famotidine there is a dosage

related effect for three of five measures. The sixth, number of episodes would not be expected to be altered.

A variety of subanalyses [36] were made notably to examine whether treatment became more or less effective as time passed, with no differences observed, and whether treatment was effective in those with meal related symptoms, famotidine 10 mg and antacid proving more effective than placebo. A range of concomitant factors was also examined including age, sex, smoking and drinking habits, and characteristics of heartburn. None were found to interact.

Taken overall the data suggests that drug recipients who have symptoms of heartburn tend to have those symptoms ameliorated more by active treatment than by placebo, and that famotidine treatment may be somewhat, though not greatly, better than antacid. The degree of difference from placebo is not large, because those given placebo have more than an even chance of doing well.

Differences did not seem to arise from lack of initial comparability of treatment groups, and therefore may reasonably be ascribed to the treatment themselves. At least in the first study those receiving 10 and 20 mg of famotidine fared somewhat better, and equivalently better than famotidine 5 mg and antacid groups.

Symptoms treated were of heartburn which ordinarily responded to antacid. Such symptoms could occur in relationship to meals or at other times. Subanalyses suggested drug efficacy for meal related symptoms as well as overall [36].

3.2. Study 2 [18]

3.2.1. Design of Study

The protocol was constructed on essentially the same lines as that of the first trial [17], with randomization to placebo, antacid, and famotidine 10 and 20 mg (but not 5 mg) when symptoms occurred. Studies were conducted blind after a week's run-in, as previously, but endoscopic and manometric studies were not performed.

3.2.2. Study Results

Those studied were essentially comparable in terms of age, sex, smoking and drinking habits and symptom patterns (Table 4).

3.2.3. Efficacy Results

The second study, conducted in 509 patients, gave similar but less clear-cut results (Table 5). Famotidine 10 and 20 mg on global evaluation gave global results of good or excellent in, respectively 77 and 80% of patients compared with 61% of placebo recipients, and 76% of antacid recipients. Data were analysed per protocol in 443 (91%) of patients. More episodes were also relieved by the active treatments, and less of these than placebo were followed by back-up treatment, though not all results were statistically significant. Other results (% of episodes requiring remedication and time to relieve first episode) showed no significant differences although, surprisingly, less episodes occurred in famotidine recipients.

3.3. Critique of Results

There is general uniformity showing evidence of drug efficacy compared with placebo, but with little difference from antacid. Examination of the data suggests that differences are unlikely to derive from maldistribution of individuals with particularly severe symptoms since individual treatment subgroups look broadly comparable. Evidence of efficacy also derives from a range of measures studied, and seems unlikely to reflect selection of particularly favourable criteria.

In the first study [17], there was reasonably convincing evidence (Table 3) that famotidine 10 mg and 20 mg were more effective than famotidine 5 mg and antacid, which were, in turn, better than placebo. In the second study [18] famotidine 10 mg was as effective as antacid, and better than placebo, and famotidine 20 mg was little superior (Table 5).

It should be noted that placebo recipients often fared very well, reflecting both placebo responses and the self-limited nature of symptoms.

Results are presented for the evaluable cohorts of 475 (84%) and 443 (91%). It is not possible to tell what happened to the remainder. Dropout rates, deduced from comparison of the evaluated cohorts with the groups entered, were low, and did not differ materially between treatment sub groups, except for a somewhat higher number in the famotidine 10 mg group in study 1 (Tables 6 and 7). This difference occurred in only one study and was not matched by a high dropout rate for the 20 mg dose; it therefore probably represented chance variation.

The proportions of patients found to have more than minimal degrees of oesophageal abnormality endoscopically [17] were, at first sight, surprisingly high. However, it should be remembered that those treated were from a group who already had a symptom commonly (though not always) referred to the gullet. The frequency of overt ulcer is also unsurprising since heartburn is commonly associated with ulcer.

3.4. Other Studies of Symptom Relief After Provocative Meals

Five such studies [19,20,21,22,23] were initially carried out and Table 8 sets out the main design features.

3.4.1. Crossover Studies [19,20,21,22]

These were essentially to the same design, though details varied. Selection criteria were of successful antacid use to treat heartburn three or more times a week with specific foods identified to cause heartburn. Those selected were given a meal claimed to induce symptoms and those doing so within 1½ hours entered the double-blind phase.

Analysis of two studies (025 and 022) [22,20] suggested confounding by carryover effects and a further, study (031) [23] was carried out using a parallel design.

Symptoms were recorded every 15 minutes for 5 hours after a test meal with drug or placebo being administered before the meal, and open treatment with known antacid being permitted in the 5-hour period after the meal if symptoms occurred.

3.4.1.1. Results

Table 9 summarises outcomes for global efficacy and for need for back-up antacid, other measures showing similar trends. Global efficacy was always greater with active drug than placebo and other measures tended as might be expected to run in parallel. Analysis of one study (025) [22] was complicated by carryover effects and so is unreliable. However the general impression gained is that treatment was effective with some, though not totally convincing, evidence of a dose response relationship. Treatment also seemed to be more effective if given 1 hour before a provocative meal than at the time.

4. Review of Safety

4.1. Clinical Findings in Studies to Support Over-the-Counter and Prescription Use [24]

Table 10 summarises findings in the 2996 individuals studied during the development of data designed to support over the counter use. Summaries of the studies appear in Appendices A and B. Based on information received from Merck Research Laboratories, these studies have been conducted in accordance with all applicable Good Clinical Practice regulations and guidelines and internal Merck Research Laboratories procedures in force at the time for these studies. There were no serious clinical or laboratory adverse responses which were considered drug related. 1824 of these were specifically studied for symptomatic responses (766 male and 1058 female) with ages ranging from under 35 (541 between age 17 and 35) to over 64 (104 between ages 64 to 84). Details of serious adverse events reported in two subjects and of reasons for stopping drug in five individuals are given in Table 11. These were not considered matters of concern.

Table 12 summarises reports of adverse events in placebo, antacid and famotidine recipients. Nervous digestive and respiratory complaints featured most commonly, but with no consistent increases in the famotidine treated over placebo and antacid recipients. The general pattern is reassuring and does not suggest significant drug related disease. No other events were recorded in more than 1% of treated groups. There was no evidence of dose relationships.

Data can be expanded by taking account of results obtained in previous studies carried out in establishing drug use by prescription. 4966 patients received treatment for periods up to and over a year, most receiving 40 mg daily for 8 to 30 days [1486] or 31 to 90 days [1466 patients] with ages ranging from 17 to 96, mean 46 years, and including 576 aged 65 and over.

Patterns of adverse responses with famotidine and placebo are shown in Tables 13 and 14. There is in Table 13 a close similarity to results in the OTC studies with no evidence that active treatment was associated with particular events. Six fatal and 66 nonfatal serious events were noted during these trials. None of the fatal or nonfatal serious events appeared definitely or probably treatment related (Table 14).

4.2. Laboratory Findings in Studies to Support Over-the-Counter and Prescription Use [24]

Studies conducted in the OTC protocol were limited, and no serious events were detected (Table 10). It therefore makes more sense to look at the much larger set of data collected during investigation for prescription use. Table 15 gives details of

serious events in the 4966 patients so reported. No event, except abnormal liver function, was observed more than once.

Only two events were considered drug related. However, attributing causality must always be difficult. Thus the finding of abnormal liver function in 4 individuals could represent real drug related disease, or coincident alcoholic or viral hepatitis. Whichever is true, there were no cases of death from severe hepatitis and findings generally showed only moderate abnormalities.

4.3. Postmarketing Studies [24]

There have been 31 studies conducted in a total of 71,607 patients. Attributing causality in such studies causes inevitable problems. 243 serious events were reported, and 95 were thought to be caused. Events reported at least five times worldwide are shown in Table 16 by frequency, together with deaths recorded more than once. Those events or deaths which appear particularly frequently include bone marrow disorders, liver dysfunction, rash and neuropsychiatric reactions.

4.3.1. Haematology [24]

Thrombocytopenia and agranulocytosis or pancytopenia have been recorded rarely as adverse effects of histamine H_2 antagonists, including famotidine.

Experience in clinical trials and in studies conducted to support over-the-counter use was reassuring, but the body of evidence is intrinsically too small to exclude the occurrence of a rare adverse response of this, or any other, type.

Fifty-nine cases of haematological adverse effects have been noted in postmarketing experience in 71,607 patients in all countries, these being possible significant effects (Table 17).

Causation is always hard to assess but the accompanying table categorizes as unlikely (other disease could well explain), possible (multiple treatments in use), probable (single treatment with famotidine only), and coincidental.

Fourteen of the 59 events seem to have occurred during single treatment, and if these are all assumed to be caused (only one case was labelled as "idiopathic") it is likely that risk is overstated. On the other hand, some of the 20 on multiple treatments may have been caused. A reasonable scenario might be to relate the 14 to treatment.

Examination of dosage data in the whole group developing thrombocytopenia, agranulocytosis or pancytopenia (irrespective of coincident drug intake or other factors) indicates that only two of the whole group received a total dose of less than 200 mg -- a likely OTC peak dose that might be used.

4.3.2. Liver Dysfunction [24]

Clinical trial data obtained in establishing prescription use and in justifying OTC use have provided a database of 6,790 treated individuals. In these, severe clinical disease were not recorded. However, this reassuring pattern is not enough to exclude occasional severe adverse events. Formal postmarketing studies in 71,607 patients give a large base but have major weaknesses through lack of knowledge of reporting rates (probably low) and difficulty in establishing causality. Four reports of disordered liver function emerged during 4966 treatment courses in establishing prescription use, with a fifth in treating Zollinger Ellison syndrome. No significant liver disease seemed to have been reported during OTC dosing studies.

Liver enzyme changes, hepatitis and cholestasis have been reported postmarketing in 16, 18 and 20 instances, respectively, but only 4, 7 and 3 were thought attributable.

Culpability is hard to determine. Concurrent alcohol consumption must account for some, and hepatitis A, B, or C for others. There seem to have been no deaths clearly related to drug ingestion, and in none, whatever the levels of believed culpability, was the dose in total taken 200 mg or less (although the data set is small). Significant risk seems unlikely.

4.3.3. Neuropsychiatric Reactions [24]

Confusion, reversible on stopping treatment is described with H_2 antagonists, mainly cimetidine treatment. However, the condition has accompanied intravenous drug use typically in severely ill individuals receiving intravenous H_2 antagonists, usually with other treatments. Overall, examination of data suggests that it is very unlikely that over-the-counter uses of oral famotidine are associated with risk. Though it should be noted that headache seems an occasional risk with all H_2 antagonists.

4.3.4. Rash [24]

In general, it is had been rare and Stevens Johnson Syndrome is undescribed.

4.4. Other Possible Risks

Those to consider include risks of precipitating cardiac disease, those associated with coincident drug intake, and use in pregnancy. In addition, it is pertinent to consider the margin of overall safety, and safety in overdose, in the elderly and in use with hepatic and renal dysfunction.

4.4.1. Cardiac [24]

Histamine receptors are demonstrable in the heart and H_2 receptors are inotropic. Hypotension, arrhythmias and asystole have been demonstrated during H_2 receptor antagonist use, predominantly cimetidine and ranitidine, and almost all intravenous use in critically ill people.

In all there have been 251 reports of "serious" cardiovascular events on famotidine, including 43 heart failure and 35 arrhythmia, which are considered in more detail below. The most common (Table 18) was myocardial infarction, but it seems likely that the occurrence of this and of other cardiac disease represents either coincidence or disease mistakingly treated as gastrointestinal (e.g., angina).

4.4.1.1. Heart Failure [24]

Only 1 of the 43 (case 14) [24] appeared to have had an episode of heart failure in the absence of co-existent cardiac or severe other disease. The overwhelming likelihood is that famotidine treatment was coincidental not causal.

4.4.1.2. Arrhythmiae [24]

Apart from occasional reports of sinus brady or tachycardia all had evidence of serious coexistent cardiac or other disease. Two cases (18 and 35) seem to have had isolated arrhythmias stopping on stopping treatment - note case 18 is case 14 of the heart failure series. It seems very unlikely that the drug poses significant risks. Conclusions of insignificant risks are supported by three intravenous and five

oral studies of cardiac function during drug use. Only one (interestingly the subject of multiple reports) claimed to detect any changes.

4.4.2. Coincident Drug Intake [9,24]

Famotidine does not interfere with hepatic cytochrome P450 activity and important drug interactions have not been detected on other bases. It is sensible, nevertheless, to consider whether H_1 antihistamines (which are available for OTC use), simple analgesics or alcohol, all as substances freely available to the takers of OTC famotidine, could be hazardous.

4.4.2.1. Astemizole and Terfenadine [24]

Arrhythmias have been reported with these OTC H_1 antihistamines. There are no reports of such events during coincident famotidine use.

4.4.2.2. Paracetamol

There is no coherent evidence to suggest toxicity is affected.

4.4.2.3. Aspirin

By raising intragastric pH, famotidine use should protect against damage.

4.4.2.4. Alcohol

Famotidine does not inhibit alcohol dehydrogenase [30,31,32,33].

4.4.3. Pregnancy

Data are limited. Teratogenesis has not been suggested by conventional testing. Experience documenting successful and uneventful pregnancy exists but is small in amount [24].

4.4.4. Margin of Safety

4.4.4.1. Toxicology Studies

The oral LD_{50} in rodents is greater than 3000 mg/kg and the minimal lethal dose in dogs is 2000 mg/kg. The difference from the dose used clinically or intended OTC is large [37].

4.4.4.2. High Dose Use in Man

Doses up to 800 mg/day have been given in the Zollinger-Ellison syndrome without ill-effect [24].

4.4.4.3. Overdosage in Man

Data included in the dossier document [37]. Seventy-four cases of overdose have been recorded in the USA, and with follow-up information is 55. There were no deaths, no major effects and in most cases (34) no effect at all, with minor effects (unspecified) in 14 or effects not related to exposure in 3. In four other suicide attempts any effects seemed likely to be attributed to other agents in use.

4.4.5. Use in the Elderly

There is no clinical or pharmacokinetic evidence to suggest drug accumulation or abnormal effects in the elderly during oral treatment, although (other) intravenous histamine H_2 antagonist use has been associated with reversible confusional states [24].

4.4.6. Use in Hepatic Dysfunction

Plasma half-life is only prolonged in uncompensated cirrhotics [24].

4.4.7. Renal Failure

Drug is excreted by the kidneys and therefore elimination will be slowed by renal disease. There is no evidence that this has caused harm [24].

5. Summary

There is good evidence that famotidine is at least as effective as antacid, and better than placebo, in ameliorating, or preventing heartburn, particularly if given an hour before a provocative meal. Choice of a dose is somewhat arbitrary, but the 10 mg level chosen by the manufacturers seems reasonable. Apart from evidence of symptomatic response there is good evidence of a rational basis in inhibition of acid secretion.

Safety of any drug cannot be assumed. The safety record of all histamine H_2 antagonists is excellent, but they are in general associated with occasional precipitation of headache, and probably causing, skin rash, liver dysfunction and bone marrow depression. All of these seem likely to be rare and probably much rarer than gut bleeding caused by aspirin, the hepatotoxicity of paracetamol and the gastrointestinal toxicity of ibuprofen. Absolute safety cannot be assumed but if these are reasonable yardsticks then the likelihood is of a better safety profile. Safety in pregnancy is an inevitable issue, and again cannot be assumed, but there is no evidence of harm resulting from the many millions of treatment courses given so far.

It is important that serious disease is not masked in presentation or altered harmfully in behaviour by treatment. Some patients who self-medicate will inevitably have in particular, undiagnosed peptic ulcers or gastric cancer.

There is no evidence to suggest that in ordinary clinical use H_2 antagonists alter adversely the behaviour of ulcer. In general the underlying disease follows its natural course. Worries have been expressed about either the carcinogenic potential or the ability to mask existing cancer of H_2 antagonists. There is good evidence from prolonged postmarketing surveillance to suggest that gastric cancer is not induced [35]. Dyspepsia in cancer could be relieved by drug use, but only whilst drug is taken. Short courses of OTC drug seem unlikely to have significant effects. Clinical observation indicates that gastric cancer progresses slowly - over several years - and it is hard to believe that OTC recommended dosage regimes would affect outcome.

6. Conclusions

6.1. Efficacy

The data presented develop a sound basis for over-the-counter drug use in that a set of indications which is readily understandable by the ordinary citizen has been shown to be ameliorated by treatment. There is little reason for believing that self treatment will delay the presentation of serious disease [34]. Self medication cannot be expected to suppress more than temporarily symptoms arising from disease, and that time period being very short in relation to disease natural history.

6.2 Safety

Histamine H_2 antagonists in general, including famotidine, have an excellent safety record in prescription use. Few adverse effects have been confidently linked with treatment, and these rarely.

6.2.1. Headache

All H_2 antagonists occasionally seem to precipitate it, and a warning is appropriate.

6.2.2. Blood Dyscrasias

Definitive evidence is hard to obtain but there is probably a (rare) risk of thrombocytopenia or marrow depression with prescription drug use. Whether this is a real risk with occasional self treatment is difficult to determine; a guess suggested it will be extremely rare.

6.2.3. Liver Dysfunction

Distinguishing occult liver disease due to other causes or alcohol is difficult. If there is a risk it is probably very small. Most recorded instances seem to have been of minor hepatic dysfunction and on this basis over-the-counter occasional treatment would seem unlikely to present a serious risk.

6.2.4. Cardiac Dysrhythmia

It seems unlikely that the low oral dosages proposed pose risks.

6.2.5. Pregnancy

Data are inadequate. Safety seems likely, but cannot be assured. A warning is appropriate - perhaps, on the lines of those for other OTC medicines since indications of hazard are lacking.

6.2.6. Overall

The case for licensing famotidine is good, but is not absolute; it can be argued that antacids are a safe, effective alternative, although may cause diarrhoea and may interfere with drug absorption or pose risk in those with kidney failure.

Famotidine has been widely and safely used and has particular advantages in its class in freedom from effects on hepatic drug metabolism, at androgen receptors and from possible effects on alcohol handling.

The suggested package insert seems sensibly worded and, in general conforms with trial results. Though I would wonder if a lower age limit of 16 might not be unreasonable. In addition, a headache warning would seem appropriate as would specific advice to the middle-aged and elderly to consult a doctor about newly emerged symptoms or where there is unexpected weight loss.

TABLE 1

Comparability A
General Features [17]

Study 1
(U17)

	Mean Age	% Male	Smokers	Drinkers	Daily Heartburn
Placebo n = 111	43.3	54.1	31.5	10.8	84.7
Antacid n = 113	45.3	49.6	25.7	8.9	74.3
Famotidine 5 mg n = 113	44.7	58.4	31.9	13.3	74.3
Famotidine 10 mg n = 113	43.5	49.6	17.7	12.4	79.7
Famotidine 20 mg n = 115	43.7	59.1	27.8	11.3	86.1

TABLE 2

Comparability B
Endoscopic and Manometric Features [17]

Study 1
(017)

	% with:-			
	Oesophagitis None or Grade 1	Gastric or Duodenal Ulcer	Gastritis or Duodenitis	Normal Sphincter Pressure
Placebo n = 111	60.4	4.5	45.9	86.5
Antacid n = 113	58.4	8.8	60.2	87.6
Famotidine 5 mg n = 113	59.3	5.3	58.4	87.6
Famotidine 10 mg n = 113	60.2	6.2	47.8	88.5
Famotidine 20 mg n = 115	60.9	4.3	54.8	86.1
Total 565				

TABLE 3

Efficacy [17]

Study 1
(017)

	Global Efficacy % Good/Excellent	% Episodes Relieved	% Requiring Back-up Treatment	% Requiring No Retreatment	Statistical Differences In Time to Relief	No. of Episodes Treated Per 14 Day Period for Full Study
Placebo	60	43	41	59		11.03
Antacid	69	63*	32**	66	*	11.16
Famotidine 5 mg	69*	61*	33*	67		11.17
10 mg	74*	71***	22***	76**	*	11.39
20 mg	75**	70***	25***	69		10.95

* P<0.05 vs. placebo

** P<0.01 vs. placebo

*** P<0.001 vs. placebo

TABLE 4

Comparability
General Features [18]

Study 2
(019)

	% with				
	Mean Age	% Male	Smokers	Drinkers	Daily Heartburn
Placebo n = 128	46.9	51.6	17.2	10.2	72.7
Antacid n = 126	44.7	46.8	17.5	10.3	71.4
Famotidine 10 mg n = 125	46.2	47.2	20.0	8.8	63.2
Famotidine 20 mg n = 130	46.1	43.8	28.5	9.2	71.5
Total 509					

TABLE 5

Efficacy [18]

Study 2
(019)

	Global Efficacy % Good/Excellent	% Episodes Relieved	% Requiring Back-up Treatment	% Requiring No Retreatment	Statistical Differences In Time to Relief	No. of Episodes Treated Per 14 Day Period for Full Study
Placebo	61	64	35	78		9.93
Antacid	76*	74+	22*	78		9.64
Famotidine 10 mg	77*	75+	23*	83		9.15**
Famotidine 20 mg	80***	75	23	83		9.32*

\+ 0.05 ≤ p <0.10 vs placebo
* P<0.05 vs. placebo
** P<0.01 vs. placebo
*** P<0.001 vs. placebo

TABLE 6

Evaluated Cohort [17]

Study 1
(017)

	Entered	Evaluated	Not Evaluated	% Evaluated
Placebo	111	96	15	86
Antacid	113	99	14	88
Famotidine 5 mg	113	97	16	86
Famotidine 10 mg	113	94	19	83
Famotidine 20 mg	115	105	10	91
	565			

TABLE 7

Evaluated Cohort [18]

Study 2
(019)

	Entered	Evaluated	Not Evaluated	% Evaluated
Placebo	128	113	15	88
Antacid	126	112	14	89
Famotidine 10 mg	125	112	13	90
Famotidine 20 mg	130	115	15	88
	509			

TABLE 8

Meal Provocation Studies

Study	Design	Treatments	No. Treated	
3 [21] 024	Double-blind Crossover	Placebo Famotidine 5,10,20 mg[b]	102	
4 [19] 020	Double-blind Crossover	Placebo Famotidine 5,10,20 mg[a]	121	X
5 [22] 025	Double-blind Crossover	Placebo Famotidine 5,10,20 mg[a]	105	X
6 [23] 031	Double-blind Parallel	Placebo Famotidine 5,10 mg[a]	493	X
7 [20] 022	Double-blind Crossover	Placebo Famotidine 5,10,20 mg[b]	105	

[a]Taken 1 hour before the meal.
[b]Taken immediately before the meal.

TABLE 9

Global Efficacy % Good or Excellent [36]

Treatment					
	One Hour Before Meal			Immediately Before Meal	
Study:	020	025	031[A]	022	024
Placebo	38	48	49	48	15
Famotidine 5mg	57***	58[a]	57*	55[a]*	26*
10 mg	55***	65[a]***	66***	52[a]**	24**
20 mg	62***	64[a]*	-	49[a]	26*
Use of Back-up Acid					
Placebo	37	35	35	16	73
Famotidine 5 mg	17***	26[a]	27	7*	61*
10 mg	18***	22[a]**	19**	10	68
20 mg	18***	23[a]*	-	13	69

A First meal only
a Carryover effect
* P<0.05 vs. placebo
** P<0.01 vs. placebo
*** P<0.001 vs. placebo

TABLE 10

Adverse Effects Recorded with Famotidine During Studies Conducted to Support Over-the-Counter Drug Use

	Clinical			Laboratory				
Study	No. of Serious Adverse Effects	Drug Related Serious Adverse Effects	No. of Adverse Effects for Which Drug Was Stopped	No. of Serious Adverse Effects	Drug Related Serious Adverse Effects	No. of Adverse Effects for Which Drug Was Stopped	Total Treated	Total Entered
017 (Trial) [17]	1	0	0	0	0	0	530	565
019 (Trial) [18]	0	0	3	0	0	0	479	509
031 (Trial) [23]	0	0	0	x	x	x	487	493
025 (Trial) [22]	1	0	1	x	x	x	102	105
022 (Trial) [20]	0	0	0	x	x	x	102	105
024 (Trial) [21]	0	0	0	x	x	x	101	102
020 (Trial) [19]	0	0	0	x	x	x	114	121
039 (Taste test) [25] 2 doses	0	0	1	x	x	x	538	540
040 (Taste test) [26] 2 doses	0	0	0	-x	-x	-x	358	360
044 (Bio equiv) [28] 2 doses	0	0	0	0	0	0	18	18
016 (Dose resp) [1] 4 doses	0	0	0	0	0	0	10	10
021 (Dose resp) [4] 6 doses	0	0	1	0	0	0	18	20
026 (Dose resp) [27] 3 doses	0	0	0	0	0	0	18	18
035 (Bio equiv) [13] 3 doses	0	0	0	0	0	0	15	15
036 (Bio equiv) [29] 3 doses	0	0	0	0	0	0	15	15

[x] No laboratory safety monitoring performed.

TABLE 11

Events Considered Serious, and Nonserious Events Leading to Discontinuation of Over-the-Counter Studies [24]

Study	Dose	Event	History
Serious Events Leading to Discontinuation			
017 (1 subject two events)*	5 mg [46 M]	Tachycardia Coronary Atherosclerosis	Known hypertension Underwent bypass Graft
025	10 mg [61 M]	Chest pain	Considered not drug related
Nonserious Events Leading to Discontinuation			
019	20 mg [40 F]	Headache	
019	20 mg [55 F]	Dizziness Premature ventricular beats	
019	10 mg [38 F]	Abdominal chest and back pain	Uterine mass found
021	20 mg [31M]	Headache, nausea, vomiting	
039	10 mg [64 F]	Dizziness, syncope, tachycardia	
* Treatment not discontinued.			

TABLE 12

Overall Patterns of Adverse Responses During OTC Studies [24]

Body System	Famotidine	Antacid	Placebo
Body as a Whole/ Site unspecified	2.7 (0.6)	3.1 (0)	1.9 (0.6)
Cardiovascular	0.3 (<0.1)	1.6 (0)	0.2 (0)
Digestive	5.4 (2.4)	6.6 (1.2)	4.2 (2.1)
Diarrhoea	1.4 (0.5)	1.6 (0.4)	0.7 (0.2)
Nausea	1.4 (0.7)	1.9 (0.4)	1.2 (0.8)
Nervous	11.1 (4.0)	8.9 (0.8)	13.2 (5.3)
Dizziness	1.5 (1.1)	0.8 (0)	1.9 (1.6)
Headache	9.8 (3.3)	7.0 (0.4)	11.9 (4.1)
Respiratory	3.3 (0.1)	9.3 (0)	4.1 (0.2)
Upper resp. infection	1.3 (0)	3.1 (0)	1.3 (0)
Musculoskeletal	1.7 (<0.1)	3.5 (0.4)	2.7 (0)
Skin	0.8 (<0.1)	1.6 (0)	1.2 (0.4)
Special Senses	0.6 (0.3)	1.6 (0)	0.6 (0.1)
Urogenital	0.8 (<0.1)	0.8 (0)	1.1 (0)
Blood	0 (0)	0.4 (0.4)	0.1 (0.1)
	2350	257	857

(Figures in brackets denote responses considered treatment related.)

TABLE 13

Overall Patterns of Adverse Responses During Famotidine Clinical Trials [24]

Body System	Famotidine	Placebo
Body As a Whole/ Site unspecified	4.3 (0.6)	5.7 (1.5)
Abdominal Pain	1.4 (0.2)	2.3 (0.7)
Cardiovascular	0.9 (0.1)	1.1 (0.1)
Digestive	8.1 (2.0)	8.1 (2.2)
Diarrhoea	1.8 (0.7)	1.3 (0.4)
Nausea	1.2 (0.2)	1.5 (0.7)
Nervous	8.8 (2.4)	9.1 (2.5)
Dizziness	1.3 (0.5)	1.0 (0.2)
Headache	5.6 (1.3)	6.0 (1.5)
Respiratory	6.0 (0)	5.3 (0.2)
Upper Resp. Infection	1.9 (0)	1.7 (0)
Musculoskeletal	2.7 (0.3)	3.1 (0.2)
Skin	2.0 (0.8)	2.2 (0.6)
Special senses	1.0 (0.2)	1.3 (0.4)
Urogenital	1.4 (0.1)	1.5 (0.1)
Blood	0 (0)	0.1 (0)
n	4966	1630

(Figures in brackets denote responses considered treatment related.)

TABLE 14

Pertinent Serious Adverse Events [24]

a) Fatal Serious Events During Clinical Trials

	Dose	Study Day	Cause	Investigator's Perceived Relation to Drug
1. F 62	40 mg	359	Natural causes	Probably None
2. M 46	20 mg	192	Suicide by firearm	Definitely None
3. M 67	20 mg	28	Cancer of lung	Definitely None
4. M 69	20 mg	1	Cancer of lung	Definitely None
5. M 71	20 mg	70	Myocardial infarct	Definitely None
6. M 58	40 mg	35	Shock	Definitely None

All rates as definitely not except case 1, probably not related.

b) Nonfatal Serious Events

	Relationship
36*	Definitely none
25**	Probably none
3***	Possible
0	Probable
0	Definite
2	Unclear
66	

* Malignant neoplasm 4, chest pain 2, myocardial infarct 2, fracture 3 intestinal obstruction 2, pneumonia 2. All others one only.

** Cerebrovascular accident 3, GI bleed 3, chest pain 3, nausea 2, abdominal pain 2, haematemesis 2. All others one only each.

*** Myositis, grand mal seizure, GI haemorrhage, one each.

TABLE 15

Serious Laboratory Events in Treated and Placebo Patients [24]

	Famotidine	Placebo
n =	4966*	1630
Serious Events	10	1
Drug Related	1	1
Treatment Group:	Hyperamylasaemia 1, Thrombocytopenia 1, Bacteremia 1, Abnormal liver function 4, Raised Alkaline Phosphatase 1, Leucocytosis 1, and Hypokalaemia 1	

* Excludes studies of Zollinger-Ellison syndrome with one serious event in 26 treated subjects (abnormal liver function)

TABLE 16

Serious Adverse Responses Reported and Related to Treatment Postmarketing at Least Five Times [24]

	Events
Psychic and psychotic reaction	24
Hepatitis	15
Thrombocytopenia	14
Rash	13
Seizure	10
Fever	8
Lack of response	7
Dizziness, GI haemorrhage, vomiting, pneumonia, gynaecomastia, bone marrow depression (each)	6
Chest pain, pancytopenia, cholestasis (each)	5
	Deaths
Bone marrow depression	4
GI bleed	2
Pancytopenia or thrombocytopenia	2
All other causes one each	24
	32

TABLE 17

Haematological Adverse Events Reported
During Postmarketing

A.	Unlikely to Be Related	
	Simple anaemia without other features	15
	Liver disease plus thrombocytopenia	4
	Multiple sepsis + low blood counts	2
	Thrombocytopenia pre-existing	1
	Developed disease 2 months later	1
	Coincident azathioprin	1
		24
B.	Possibly Related	
	Multiple treatments often for multiple conditions	
	Thrombocytopenia	8
	Leuko or pancytopenia	12
C.	Probably Related	
	Single treatment	
	Thrombocytopenia	8
	Leukopenia	5
	Haemolysis	1
D.	Coincident Disease	
	Idiopathic thrombocytopenia	1

Definitions from Section 4.3.1. applied to [24].

TABLE 18

Reports of Serious Cardiovascular Events During Investigational and Marketed Drug Use [24]

Myocardial Infarction	62
Heart Failure	43
Arrhythmia	35
Cerebrovascular Accident	25
Angina Pectoris	21
Pulmonary Embolism	12
Hypertension and Shock (Each)	9
Hypotension	7
(All Others four or less)	

[redacted]

5

Product	Blocazide	Code	
Item	Patient Information Leaflet		
Based on			
Typist	[redacted] (S:FAMOTC.PIL)	Date typed	15.01.93
Writer	[redacted]	Reade	[redacted]
Technical Approval	[redacted]	Date	[redacted]
Legal Approval	[redacted]	Date	[redacted]

Blocazide™

(famotidine)

WHAT IS IN THE TABLETS?

Each tablet contains 10 mg of famotidine as the active ingredient. They also contain: Hydroxypropylcellulose EP, Methylhydroxypropylcellulose EP, Red iron oxide EP, Magnesium stearate EP, Microcrystalline cellulose EP, Pregelatinised maize starch BP, Talc EP, Titanium dioxide BP.

This pack contains ?? tablets.

HOW DO THE TABLETS WORK?

'Blocazide' is a new therapy that provides rapid relief from indigestion and heartburn with just one small tablet. It has been clinically proven to control excess stomach acid for up to nine hours. Unlike antacids which neutralise acid, 'Blocazide' contains famotidine, an ingredient that actually controls the flow of excess acid and treats the cause of pain and discomfort. 'Blocazide' is available in easy-to-swallow tablets.

Continuation Sheet Number 2

Product	Blocazide	Code
Item	Patient Information Leaflet	

Product licence holder:

Merck Sharp & Dohme Limited

Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU

Manufacturer:

Name

Address

WHAT ARE 'BLOCAZIDE' TABLETS USED FOR?

'Blocazide' Tablets are for the treatment of indigestion, acid indigestion, nervous indigestion, heartburn, dyspepsia, acidity, and symptoms of upset stomach.

CHECK BEFORE YOU TAKE THIS PRODUCT

Ask your doctor before taking the tablets if you are pregnant or breast-feeding.

HOW SHOULD YOU TAKE 'BLOCAZIDE'?

Adults, and children 12 years of age or older:

- **Take 1 tablet as needed to relieve indigestion, acid indigestion, nervous indigestion, heartburn, dyspepsia, acidity, and symptoms of upset stomach, or 1 tablet one hour before eating to relieve symptoms usually associated with food and drink.**
- **Repeat the dose if symptoms persist, up to a maximum of 2 tablets in a 24-hour period.**
- **Do not take for more than two weeks except on the advice of your doctor.**

Continuation Sheet Number 3

Product	Blocazide	Code
Item	Patient Information Leaflet	

Also, consult your doctor promptly if you have difficulty swallowing, or persistent stomach pains.

WILL THE TABLETS SUIT YOU?

Most people do not suffer side effects when taking 'Blocazide'. If you think you are reacting badly in any way, stop your treatment and see your doctor.

STORING YOUR TABLETS

'Use by' date: Do not use 'Blocazide' Tablets if they are past the expiry date on the box.

Remember: Keep all medicines out of the reach of children.

Date of first printing ...

2 LABELLING

2.1 Film-coated Tablets

The following text will appear on the cartons for the blister packs, and the label for the bottles:

FRONT PANEL:

New
BLOCAZIDE™
ACID CONTROLLER
Rapid Relief from Indigestion and heartburn.
BLOCAZIDE™ has been clinically proven to control excess stomach acid for up to 9 hours.
'X' tablets

BACK PANEL:

BLOCAZIDE™ Tablets
Famotidine 10 mg

For the treatment of indigestion, acid indigestion and nervous indigestion, heartburn, dyspepsia, excess acid and upset stomach.

DOSAGE: Adults and children over 12 years: Take one tablet as required, or for symptoms usually associated with food and/or beverage take one tablet one hour before eating. Repeat if symptoms return, up to a maximum of 2 tablets in a 24-hour period.

If symptoms persist for more than 2 weeks, consult your doctor.

Do not take if you are pregnant or breast-feeding except on a doctor's advice.

If you have difficulty swallowing, or persistent abdominal discomfort, consult your doctor.

Inactive Ingredients: Red Iron Oxide and Titanium Dioxide.

Keep all medicines safely away from children.

'X' tablets

P

Product Licence No: 0025/0312
Product Licence Holder: Merck Sharp and Dohme Ltd Dist by: JJ/MSD*
Hertford Road
Hoddesdon
Herts En11 9BU

™ Trademark

Company logo

Bar code

BASE PANEL:

BLOCAZIDE™
ACID CONTROLLER

Expiry date:
Batch No:

SIDE PANELS:

BLOCAZIDE™
'X' tablets

TOP PANEL:

BLOCAZIDE™
ACID CONTROLLER
'X' tablets

Note:

The distributor may or may not be included

'X' refers to the number of tablets

NUMBER:

PL 0025/0312

COMPANY:

Merck Sharp & Dohme Ltd

PRODUCT:

Blocazide 10mg Film-coated Tablets

THERAPEUTIC CLASS:

H_2-receptor antagonist

ACTIVE CONSTITUENT:

Famotidine 10mg

KEY WORDS:

POM to P

SUB-COMMITTEE ON CHEMISTRY PHARMACY AND STANDARDS

DRAFT RECOMMENDATION

On the evidence before them, the Sub-Committee recommended the grant of a Product Licence for this preparation provided that the applicant complies with the following conditions:

1. Data to compare the in-vitro dissolution profile of Blocazide 10mg Film-coated Tablets with those of Pepcid Tablets 20mg and 40mg should be provided.

2. Process validation protocols for dosage form manufacture at each of the proposed sites should be provided.

3. The finished product specification should include a test and suitable limit for moisture content.

4. The product containers should be restricted to those with child-resistant properties.

NUMBER:

PL 0025/0312

COMPANY:

Merck Sharp & Dohme Ltd

PRODUCT:

Blocazide 10mg Film-coated Tablets

THERAPEUTIC CLASS:

H_2-receptor antagonist

ACTIVE CONSTITUENT:

Famotidine 10mg

SUB-COMMITTEE ON PHARMACOVIGILANCE

APPLICATION FOR NON-PRESCRIPTION AVAILABILITY

DRAFT RECOMMENDATION

Draft advice on legal classification

The Sub-Committee considered whether Blocazide (the product) falls within a description or class specified for the purpose of section 58 of the Medicines Act 1968 by section 58A(2) of that Act, as being appropriate for supply on a prescription only basis and advised that the POM Order be amended to allow non prescription supply.

The Committee saw no reason to restrict the exemption from POM control to this particular product and recommended that the change in the POM Order be made to the entry for famotidine 10mg (the drug substance) when used for the short-term symptomatic relief of heartburn, dyspepsia and hyperacidity, in a dose of 10mg as needed to relieve symptoms, or one hour before eating for symptoms associated with food and beverage, to a maximum daily dose of not greater than 20mg for the treatment period of not greater than 2 weeks.

NUMBER:

PL 0025/0312

COMPANY:

Merck Sharp & Dohme Ltd

PRODUCT:

Blocazide 10mg Film-coated Tablets

THERAPEUTIC CLASS:

H_2-receptor antagonist

ACTIVE CONSTITUENT:

Famotidine 10mg

SAFETY AND EFFICACY SUB-COMMITTEE

DRAFT RECOMMENDATION

On the evidence before them, the Sub-Committee recommended the grant of a Product Licence for this preparation provided that the applicant complies with the following conditions:

1. The indication is restricted to "the short-term symptomatic relief of heartburn, dyspepsia and hyperacidity" only.

2. The MLA 201 and SPC should be amended to the satisfaction of the Secretariat in respect of:-

2.1 Recommended doses and dosage schedules.

Clear statements should be made regarding the treatment period as follows:-

2.1.1 The maximum treatment period is 2 weeks.

2.1.2 If symptoms persist after 2 weeks' treatment the patient must seek medical advice.

The recommendations for use in children should be revised as follows:-

2.1.3 Blocazide 10mg is recommended for use in adults and children 16 years of age or older. Blocazide 10mg is not recommended for use in children.

NUMBER:

PL 0025/0312

COMPANY:

Merck Sharp & Dohme Ltd

PRODUCT:

Blocazide 10mg Film-coated Tablets

THERAPEUTIC CLASS:

H_2-receptor antagonist

ACTIVE CONSTITUENT:

Famotidine 10mg

SAFETY AND EFFICACY SUB-COMMITTEE

DRAFT RECOMMENDATION

2.2 **Contraindications**

Blocazide should be contraindicated in:-

- pregnancy and lactation
- children under 16 years of age
- patients with moderate or severe renal failure
- patients with severe hepatic impairment
- patients under regular medical supervision for other reasons
- patients suffering from any other illness or taking other medications either physician-prescribed or self-prescribed
- patients of middle age or older with new or recently changed dyspeptic symptoms
- patients with unintended weight loss in associated with dyspeptic symptoms.

2.3 **Interactions with other medicaments**

A statement should be included regarding the potential for interaction between famotidine and antihistamines.

2.4 **Other undesirable effects**]
Use in pregnancy and lactation]

These sections should also include the statements made in the licence documentation for the previously marketed strengths of famotidine, as Pepcid.

NUMBER:

PL 0025/0312

COMPANY:

Merck Sharp & Dohme Ltd

PRODUCT:

Blocazide 10mg Film-coated Tablets

THERAPEUTIC CLASS:

H_2-receptor antagonist

ACTIVE CONSTITUENT:

Famotidine 10mg

SAFETY AND EFFICACY SUB-COMMITTEE

DRAFT RECOMMENDATION

2.5 **Special warnings and precautions**

A statement regarding the possible relationship between famotidine and haematological disorders should be made.

2.6 **Overdose**

A statement should be included regarding management in those patients who do overdose with this drug.

2.7 **Incompatibilities**

This statement should read as "none known".

3. The patient information leaflet should be amended to the satisfaction of the Secretariat in respect of:-

3.1 Those groups of patients in whom Blocazide should not be used without prior medical consultation who should be clearly stated, as listed above under 2.2.

3.2 The list of other constituents which should be completed in line with the MLA 201 form, page 7.

3.3 The occurrence of headache and dizziness and possibly gastrointestinal tract symptoms, which should be described.

NUMBER:

PL 0025/0312

COMPANY:

Merck Sharp & Dohme Ltd

PRODUCT:

Blocazide 10mg Film-coated Tablets

THERAPEUTIC CLASS:

H_2-receptor antagonist

ACTIVE CONSTITUENT:

Famotidine 10mg

SAFETY AND EFFICACY SUB-COMMITTEE

DRAFT RECOMMENDATION

3.4 The paragraph which describes "How do the tablets work?" which should be revised and the descriptors, "rapid", "small" and "easy to swallow" should be deleted.

4. The product labelling should be amended to the satisfaction of the Secretariat particularly in respect of:-

4.1 Clear marking such that the prospective patient will understand that Blocazide should not be used if he/she suffers from any other illness, is taking any other regular medicines or is being seen regularly by his/her GP or by any hospital doctor.

4.2 The use of descriptors "rapid", "acid controller" and "new" should be deleted.

4.3 The clarity of the dosage recommendations.

Labels for the blister packs for the film coated tablets should be submitted.

NUMBER:

PL 0025/0312

COMPANY:

Merck Sharp & Dohme Ltd

PRODUCT:

Blocazide 10mg Film-coated Tablets

THERAPEUTIC CLASS:

H_2-receptor antagonist

ACTIVE CONSTITUENT:

Famotidine 10mg

SAFETY AND EFFICACY SUB-COMMITTEE

DRAFT RECOMMENDATION

5. **Draft advice on legal classification**

The Sub-Committee considered whether Blocazide (the product) falls within a description or class specified for the purpose of section 58 of the Medicines Act 1968 by section 58A(2) of that Act, as being appropriate for supply on a prescription only basis and advised that the POM Order be amended to allow non prescription supply.

The Committee saw no reason to restrict the exemption from POM control to this particular product and recommended that the change in the POM Order be made to the entry for famotidine 10mg (the drug substance) when used for the short-term symptomatic relief of heartburn, dyspepsia and hyperacidity, in a dose of 10mg as needed to relieve symptoms, or one hour before eating for symptoms associated with food and beverage, to a maximum daily dose of not greater than 20mg for the treatment period of not greater than 2 weeks.

NUMBER:

PL 0025/0312

COMPANY:

Merck Sharp & Dohme Ltd

PRODUCT:

Blocazide 10mg Film-coated Tablets

THERAPEUTIC CLASS:

H_2-receptor antagonist

ACTIVE CONSTITUENT:

Famotidine 10mg

KEY WORDS:

POM to P

SUB-COMMITTEE ON CHEMISTRY PHARMACY AND STANDARDS

DRAFT RECOMMENDATION

On the evidence before them, the Sub-Committee recommended the grant of a Product Licence for this preparation provided that the applicant complies with the following conditions:

1. Data to compare the in-vitro dissolution profile of Blocazide 10mg Film-coated Tablets with those of Pepcid Tablets 20mg and 40mg should be provided.

2. Process validation protocols for dosage form manufacture at each of the proposed sites should be provided.

3. The finished product specification should include a test and suitable limit for moisture content.

4. The product containers should be restricted to those with child-resistant properties.

[redacted]

To: [redacted] **From:** [redacted]

Business C

10 November 1993

RE: Safety profile of famotidine.

I enclose a short review of the safety profile of famotidine because I understand you are dealing with a POM to P application for this drug. Business C picked up some reports of drug interactions and of breast disorders which prompted us to look into the overall safety profile further. The conclusions reached are that there are some changes required to the data sheet - these are discussed more fully below, but the changes we think appropriate are :

1 - removal of the reference to warfarin, phenytoin and theophylline in the section that deals with drug interactions.

2 - addition of a statement to the effect that breast disorders such as gynaecomastia or galactorrhea have been reported in patients taking famotidine.

The outcome of this review is that there are no major safety issues which would prevent such a move. I would be grateful if you would inform me of what happens with the famotidine data sheet.

UK Yellow Card Database - Overview.

A copy of the Drug Analysis Print (DAP) is annexed (Annex 1). Since the first report in July 1987 there have been a total of 521 reactions from 394 reports to date (October 1993). The most commeon single reaction associated with famotidine from this source is dizziness (36 cases). The next most common reactions are of headache (34), unspecified rashes (30), diarrhoea (29), nausea (25), pruritis (20), drug ineffective (19), urticaria and unspecified abdominal pain (both 16) and vomitting (11). All of these reactions are mentioned in the data sheet for famotidine.
Other reactions which have caused concern include the following which are discussed further below: breast disorders including gyneacomastia (6), breast pain (4) and breast engorgement / enlargement (1 and 2 cases respectively); oedema (8); abnormal vision (5) and drug interactions (1).

Specific Issues of Concern.

1/ Famotidine and Drug Interactions.

ADR [redacted]
This is the only case on the data base of an interaction between famotidine and another drug. It concerns a [redacted] patient who took famotidine (40 mg/d) for 4 days. She was an [redacted] taking phenytoin (dosage unknown) and [redacted] cardamazepine. Her fit frequency increased whilst on famotidine and reduced when the drug was stopped.

2/ Breast Disorders.

Concern over this issue arose from a literature report (Delpre et al., 1993) describing a patient who experienced hyperprolactinaemia and breast engorgement whilst on famotidine. The patient was a 67 year old woman who took 80 mg famotidine per day (twice the recommended daily dose) for 5 months. Towards the end of this treatment period she complained of breast pain and engorgement and her prolactin concentration was found to be 130 ng/ml (normal 5 - 10 ng/ml). Three months after stopping the drug her prolactin concentration was measured at 5.5 ng/ml and her breast symptoms had resolved. There are a number of reports of similar reactions on the yellow card database and these are summarised below.

ADR [redacted]
This is a report of a [redacted] woman who took famotidine (40 mg/d) for [redacted]. The drug was withdrawn because

ADR [redacted]

withdrawn. The final outcome of the reaction is not known.

ADR [redacted]
A [redacted] of unspecified age took 40 mg/d Pepcid and developed breast pain after 8 months on the drug. The drug was stopped and the symptoms resolved over the next month, having lasted 28 days. [redacted] other medication at the time included Temazepam, cephalexin and Kolantin.

Conclusion: As there is no warning in the data sheet about this effect and as it seems to occur in a minority of people, the data sheet should be amended to warn of possible reactions of this nature.

3/ Abnormal Vision NOS.

There are 5 cases of vision abnormalities on the yellow card database.

ADR [redacted]
A [redacted] year old [redacted] took 40 mg/d famotidine for 15 days for an unspecified indication. [redacted] developed blurred visoin 4 weeks after the drug was stopped. [redacted] other medication included Becotide, Ventolin and metoclopramide and [redacted] had previously been on ranitidine.

ADR [redacted]
A [redacted] year old man took 40 mg/d famotidine for lees than 1 month. He developed blotches in front of his eyes within the first week of treatment.The [redacted] had previously had blotchy appearances in [redacted] visual foield in the past. [redacted] also had an erythematous rash. Both symptoms resolved when the drug was stopped.

ADR [redacted]
A [redacted] year old [redacted] took 40 mg famotidine for 3 days. On the second day [redacted] developed abnormal visoin, vertigo, dyspnoea and had abdominal pain. The drug was stopped and all [redacted] symptoms disappeared within 2 days.

ADR [redacted]
An unknown individual took 20 mg/d famotidine for an unspecified timne and indication. Back pain, myalgia, dizziness, myopathy, weight decrease, thrombocythaemia and abnormal vision developed on the first day of treatment, but the drug was not withdrawn. Other medication included Inderal and Persantin.

ADR [redacted]
A [redacted] year old man took 20 mg/d famotidine for 8 months. After 6 months [redacted] complained of abnormal vision, in association with dizziness, headaches and a dry mouth: the drug was stopped, but the final outcome was not recorded.

Conclusion: Each individual case is not particularly convincing. The lack of detail in describing the nature of the abnormal visoin in most cases is also not supportive of a case to warn of this reaction. Nevertheless, the existance of 5 reports suggests that there might be a real effect. Doctors and patients have a right to know of this possible reaction.

4/ Oedema.

The famotidine data sheet warns of angioedema, but like other data sheets does not mention oedema as a possible reaction. There are a number of cases of oedema on the database.

ADR [redacted]
A [redacted] year old [redacted] took 40 mg/d famotidine for a gastric ulcer and developed oedema and pleural effusion with increases in glutamic-oxaloacetic transaminase and lactate dehydrogenase. The drug was not withdrawn and no final outcome is given.

ADR [redacted]
A [redacted] year old [redacted] took 40 mg/d famotidine for 8 weeks. She had previously been taking Zantac and continued to take gaviscon. [redacted] developed oedema, pruritis and an erythematous rash after 7 weeks on the drug which subsided 17 days after the drug had been stopped.

ADR [redacted]
A [redacted] year old [redacted] took 20 mg/d famotidine for 4.7 months. After this time [redacted] developed oedema and the drug was stopped. The oedema resolved 3 weeks after the drug was stopped.

ADR [redacted]
A [redacted] year old [redacted] took 20 mg/d famotidine for 20 days and developed oedema on the 11th day. The oedema resolved on the day the drug was stopped. The reporting doctor implicated the sodium content of her concomitant Gaviscon for the oedema.

ADR [redacted]
A [redacted] of unknown age took 40 mg/d famotidine for an unknown indication for a single day. [redacted] experienced chest pain and oedema, which resolved when the drug was stopped.

ADR [redacted]
A [redacted] of [redacted] took 40 mg/d famotidine for 4 days for an unstated indication and experienced a number of reactions including oedema, malaise, flatulence and parasthesia starting on the second day of treatment. All symptoms resolved within 1 day of the drug being withdrawn.

A [redacted] year old [redacted] took one tablet of Pepcid (20 mg, indication not known) at night and developed breast pain and enlargement within a fortnight. The drug was not discontinued and the final outcome is not known.

ADR [redacted]
A [redacted] year old [redacted] took Pepcid (dose and indication not known) and developed breast pain and enlargement after 14 months treatment . The drug was stopped because of the reaction. [redacted] other medication at the time consisted of Gaviscon (20 ml bd) and dienoestrol and Sultrin, both for atrophic vaginitis and finally Regulan, for an unspecified illness. At the time of the report [redacted] was recovering.

ADR [redacted]
A [redacted] year old [redacted] took 40 mg/d Pepcid for a gastric ulcer for 5 weeks . [redacted] developed breast pain and gynaecomastia within 3 weeks and the drug was withdrawn subsequebtly. The patient had not recovered at the time of the report, a week after the drug had been stopped. He was also taking Nardil (45 mg/d, indicatin not stated) at the same time. [redacted] had previously had gynaecomastia whilst taking cimetidine.

ADR [redacted]
A [redacted] year old [redacted] with oesophageal reflux took 20 mg/d Pepcid for 15 months. At some point in time [redacted] developed gynaeconmastia sufficient to cause the drug to be withdrawn. [redacted] other medication was bendrofluazide (5 mg/d) and senna for constipation.

ADR [redacted]
A [redacted] year old [redacted] took 20 mg/d Pepcid for 25 days for an unspecified indication. On the 17th day [redacted] developed mastitis and gynaecomastia which caused the drug to be withdrawn. [redacted] subsequently recovered over the course of the next month. No other drugs were mentioned on the report.

ADR [redacted]
A [redacted] year old [redacted] took 40 mg/d Pepcid for 7 weeks for an unspecified indication. Gynaecomastia developed a fortnight after [redacted] had stopped taking the drug. No other drugs were mentioned in the report.

ADR [redacted]
A [redacted] of unspecified age took 40 mg/d Pepcid for 10 months for an unspecified reason. [redacted] developed gynaecomastia in the 10th month of treatment and the drug was stopped. The final outcome is not known. [redacted] had also been taking indomethacin for a number of years.

ADR [redacted]
A [redacted] year old [redacted] took 20 mg/day Pepcid for 7 months for an unknown indication. After 5 months [redacted] developed gynaecomastia of the left breast and the drug was

ADR [redacted]
A [redacted] took 40 mg famotidine twice daily for 4.3 months. [redacted] developed ankle oedema after 4 weeks which lasted 3.5 months. When the drug was stopped the reaction resolved within 3 days. [redacted] other drugs iwere frusemide (120 mg/d) and amiloride (5 mg/d), both of which were commenced before famotidine was started.

ADR [redacted]
A [redacted] year old [redacted] developed paraesthesia and oedema 2 days after starting treatment of an unknown indication with famotidine (40 mg/d). The drug was stopped, but the final outcome was not known.

Conclusion: Most of these patients are quite elderly and therefore are more likely to develop oedema than younger individuals. The relevance of the drug in several of the reports is not entirely clear. With the warning that angioedema might result, there is no case for the addition of this to the data sheet on the basis of the information available at the present time.

Published Sources of Information.

A review of the literature of safety issues in relation to famotidine suggests that

1/ there might be an interaction with theophylline such that the elimination of theophylline is delayed.

2/ there are reports in the literature that famotidine potentiates phenytoin and warfarin.

3/ reports of impotence.

4/ reports of hallucinations and of confusion - there is a warning of these reactions in the US data sheet.

Conclusions From the Published Literature.

Famotidine is a very safe drug and resembles the other H2 antagonists in this respect. Action may be needed to include information on several reactions not already listed in the product information for famotidine.

[redacted]

The famotidine data sheet should not contain statements that it does not interact with phenytoin, theophylline or warfarin when there are case reports where it has been documented to do so. There is only one report on the UK Yellow Card database of a drug interaction, so there does not seem to be a large problem at present. Appropriate action is to remove phenytoin, theophylline and warfarin from the list of drugs reported not to interact with famotidine.

Secondly, the warning of hallucinations and confusion present in the US product information. This has been reported for the other H2 antagonists and the data sheets

for ranitidine has warnings about both reactions, whereas the cimetidine data sheet warns of confusion. The famotidine DAP has 5 cases of confusion and 1 of hallucinations. Despite this, I do not think that these cases on the database are sufficient to warrant a change to the data sheet.

There are 3 reports of impotence on the DAP for famotidine. In view of the non-serious nature of this reaction and the low number of cases, it is not appropriate to add this reaction to the product information.

Reference List

Andersen M, Schou JS (1993) Safety implications of Over-the-Counter avalability of H2-antagonists. Drug Safety 8: 179-185.

Aymard J-P, Aymard B, Netter P, Bannworth B, Trechot P, Streiff F (1988) Haematological adverse effects of histamine H2-receptor antagonists. Med Toxicol 3: 430-448.

Campagna KD (1991) Drug-drug interactions with H2-receptor antagonists. American Pharm NS31: 29-35.

Dal Negro R, Pomari C,Turco P (!993) Famotidine and theophylline Pharmacokinetics: an unexpected cimetidine-like interaction in patients with chronic obstructive pulmonary disease. Clin Pharmacokinetics 24: 255-258.

Delpre G, Lapidot M, Lipchitz A, Livni E, Kadish U (1993) Hyperprolactinaemia during famotidine therapy. Lancet 342: 868.

Freston JW (1989) Perspectives on safety issues and drug interactions with H2-receptor antagonists. J Drug Dev 2: (Suppl 3) 61-70.

Hansten PD (1990) Overview of the safety profile of the H2-receptor antagonists. Ann Pharmacother 24:S38-S41.

Honig PK, Wortham DC, Zamani K, Conner DP, Mullin JC, Cantilena LR (1993) Effect of concomitant administration of cimetdine and ranitidine on the pharmacokinetics and electrocardiographic effects of terfenadine. Eur J Pharmacol 45: 41-46.

Hussey EK,Dukes GE (1989) Do all histamine2-antagonists cause a warfarin drug interaction? Ann Pharmacother 23: 675-679.

Karlstadt RG, Palmer RH (1991) Unrecognized drug interactions with famotidine and nizatidine. Arch Intern Med 151: 810-814.

Mescheder A, Ebert U, Halabi A, Kirch W (1993) Changes in the effects of nizatidine and famotidine on cardiac performance after pretreatment with ranitidine. Eur J Clin Pharmacol 45: 151-156.

Schulz M (1990) Interaktionen von H2-blockern mit anderen arzneistoffen. Pharm Zeitung.11/135 p9-12

BLOCAZIDE PL 0025/0312-3 (Famotidine)

ADROIT: There are a total of 512 ADRs (1 fatal), associated with famotidine. The Drug Analysis Print for famotidine is attached. Eight of the reactions were of oedema, 1 of fatal pulmonary embolism and 3 of platelet related disorders. The majority of reports are either of generalised skin reactions or non serious gastrointestinal tract reactions.

DRUG FILE: Prescription Event Monitoring (PEM) and Post Marketing Surveillance (PMS) studies have been performed with famotidine. There were 9,519 patients recruited into the PEM study. No significant safety issues were identified. There were 8,125 patients registered on the Pepsid (famotidine) PMS study. The study was designed to monitor all medical events from the time that patients received their first prescriptions of Pepcid. Serious adverse events which were reported to the CSM during the study include 1 report of suspected pancreatitis, which was fatal, 1 report of supraventricular tachycardia and left ventricular failure and 1 report of acute retention. There is no additional information of relevance regarding ADRs on Drug File.

MONITORING LISTS: This drug is not being monitored regarding any safety issues.

There is concern regarding the product name. This bears resemblance to both beta blockers and diuretics, rather than an H2 blocker and may cause confusion. We suggest that the product name should be altered.

EXTRACTED FOR PERIOD: 01/07/63 - 27/02/93 EARLIEST REACTION DATE: 26/07/87 REACTION: ALL ORIGIN: UK

DRUG : FAMOTIDINE ROUTE: ALL SUBSTANCE/VARIANT/NPCG: SUBS

SINGLE-CONSTITUENT PRODS : PEPCID

MULTI-CONSTITUENT PRODS : NONE

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Autonomic disorders				
Cutaneous disorders				
Sweating increased	5	0	0	0
Gastrointestinal autonomic disorders				
Dry mouth	9	0	0	0
Genito-urinary autonomic disorders				
Urinary retention	2	0	0	0
SYS ORGAN CLASS TOTAL:	16	0	0	0
Cardiovascular disorders				
Cardiovascular disease symptoms & signs				
Oedema	8	0	0	0
Palpitations	3	0	0	0
Pulmonary vascular disease				
Pulmonary embolism	1	1	0	0
Hypotension (all forms)				
Postural hypotension	1	0	0	0
Cardiac arrhythmias (general)				
Arrhythmia	1	0	0	0
Extrasystoles NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	15	1	0	0
Cerebrovascular disorders				
Cerebral ischaemia (aetiology unspecified)				
Cerebrovascular accident	1	0	0	0
SYS ORGAN CLASS TOTAL:	1	0	0	0
Disorders of metabolism & nutrition				
Appetite & nutritional disorders				
Weight decrease	1	0	0	0
Weight increased	2	0	0	0
Acidotic disorders				
Lactic acidosis	1	0	0	0
Diabetes mellitus (all forms)				
Diabetes mellitus reactivated	1	0	0	0
Hyperlipidaemias				
Hyperlipidaemia NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	6	0	0	0
Disorders of the ear				
Hearing abnormal				
Deafness	1	0	0	0
Vestibular disorders				
Vertigo	4	0	0	0
SYS ORGAN CLASS TOTAL:	5	0	0	0
Disorders of the eye				
Abnormal vision (all forms)				
Abnormal vision NOS	5	0	0	0
Conjunctival and scleral disorders				
Conjunctivitis NOS	2	0	0	0
Eye symptoms & signs				
Eye irritation	1	0	0	0
Eye pain	1	0	0	0
Lacrimal gland disorders				
Xerophthalmia	2	0	0	0
SYS ORGAN CLASS TOTAL:	11	0	0	0
Gastrointestinal disorders				
Anal & rectal disorder NOS				
Rectal haemorrhage	2	0	0	0
Enteritis, colitis & proctitis (exc infections)				
Colitis	2	0	0	0
Gastrointestinal disorders NOS				
Abdominal adhesions	1	0	0	0
Gastrointestinal system symptoms & signs				
Abdominal pain NOS	16	0	0	0
Constipation	7	0	0	0
Diarrhoea	29	0	0	0
Dyspepsia	4	0	0	0
Eructation	1	0	0	0
Flatulence	4	0	0	0
Nausea	25	0	0	0
Vomiting	11	0	0	0
Ill-defined gastrointestinal infections				
Gastroenteritis NOS	1	0	0	0
Oral soft tissue disorders				
Stomatitis ulcerative	2	0	0	0
Salivary gland disorders				
Parotitis	1	0	0	0
SYS ORGAN CLASS TOTAL:	106	0	0	0
General disorders				

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Flushing	1	0	0	0
General symptoms & signs				
Chest pain	2	0	0	0
Dizziness (exc vertigo)	33	0	0	0
Fatigue	5	0	0	0
Feeling abnormal	1	0	0	0
Insomnia	11	0	0	0
Irritability	1	0	0	0
Malaise	10	0	0	0
Nightmares	6	0	0	0
Pain	2	0	0	0
Pyrexia	2	0	0	0
Rigors	1	0	0	0
Sedation	8	0	0	0
Thirst	5	0	0	0
Therapeutic & non-therapeutic drug responses				
Drug ineffective	19	0	0	0
Drug interaction NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	108	0	0	0
Haemopoietic disorders				
Platelet related disorders				
Idiopathic thrombocytopenic purpura	1	0	0	0
Thrombocythaemia	1	0	0	0
Thrombocytopenia	1	0	0	0
Disorders with decreased white blood cells				
Leucopenia NOS	1	0	0	0
Neutropenia	1	0	0	0
Disorders with increased white blood cells				
Monocytosis	1	0	0	0
SYS ORGAN CLASS TOTAL:	6	0	0	0
Hepato-biliary disorders				
Hepatic function abnormalities				
Alkaline phosphatase increased	1	0	0	0
Hepatic function abnormal NOS	1	0	0	0
Jaundice (all forms)				
Jaundice NOS	2	0	0	0
SYS ORGAN CLASS TOTAL:	4	0	0	0
Musculoskeletal, connective tissue & bone disorders				
Muscle disorders				
Muscle cramps	1	0	0	0
Myalgia	3	0	0	0
Myopathy	1	0	0	0
Musculoskeletal disorders NOS				
Back pain	2	0	0	0
Arthropathies nonspecific				
Arthralgia	6	0	0	0
Arthritis	2	0	0	0
Arthropathy	1	0	0	0
Crystal arthropathies				
Gout	1	0	0	0
SYS ORGAN CLASS TOTAL:	17	0	0	0
Neurological disorders				
Convulsions & epilepsy				
Convulsions NOS	1	0	0	0
Headache (all forms)				
Headache (except migraine)	34	0	0	0
Migraine	5	0	0	0
Impaired consciousness				
Syncope	1	0	0	0
Sensory disturbances				
Paraesthesia	7	0	0	0
Taste altered	2	0	0	0
Taste loss	1	0	0	0
Cerebellar movement disorders (acquired)				
Cerebellar ataxia	1	0	0	0
Other movement disorders (acquired)				
Gait abnormal	1	0	0	0
Hyperkinetic syndrome	1	0	0	0
Tremor NOS	1	0	0	0
Peripheral neuropathies				
Guillain Barre syndrome	1	0	0	0
SYS ORGAN CLASS TOTAL:	56	0	0	0
Peripheral vascular disorders				
Arterial inflammatory diseases				
Vasculitis NOS	1	0	0	0
Venous thrombosis & thrombophlebitis				
Venous thrombophlebitis	1	0	0	0
SYS ORGAN CLASS TOTAL:	2	0	0	0
Psychiatric disorders				
Affective disorders (all forms)				
Depression NOS	2	0	0	0
Endogenous depression	1	0	0	0
Psychiatric symptoms & signs				
Aggression	1	0	0	0
Agitation	4	0	0	0
Anxiety	1	0	0	0
Confusion	5	0	0	0
Depersonalisation	2	0	0	0
Emotional problems	1	0	0	0
Hallucinations	1	0	0	0
Nervousness	3	0	0	0
Psychoses (excluding affective psychoses)				
Paranoia	2	0	0	0

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Psychosis NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	24	0	0	0
Renal & urinary disorders				
Urinary disease symptoms & signs				
Nocturia	1	0	0	0
Polyuria	1	0	0	0
Renal colic	1	0	0	0
Urinary frequency	5	0	0	0
SYS ORGAN CLASS TOTAL:	8	0	0	0
Reproductive disorders				
Breast neoplasms				
Malignant breast neoplasm	1	0	0	0
Reproductive disorders NOS				
Libido decreased	1	0	0	0
Libido increased	1	0	0	0
Miscellaneous breast disorders				
Breast engorgement	1	0	0	0
Breast enlargement	2	0	0	0
Breast pain	4	0	0	0
Gynaecomastia	6	0	0	0
Mastitis	1	0	0	0
Nipple disorder	2	0	0	0
Disorders of menstruation				
Menorrhagia	1	0	0	0
Male sexual disorders				
Impotence	3	0	0	0
Prostatic disorders				
Prostatic disorder NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	24	0	0	0
Respiratory disorders				
Respiratory system chest symptoms & signs				
Dyspnoea	1	0	0	0
Lower respiratory tract infections (all forms)				
Chest infection	1	0	0	0
Obstructive airways disorders				
Bronchospasm	1	0	0	0
Nasal cavities & sinuses disorders (exc infections)				
Allergic rhinitis	1	0	0	0
Epistaxis	1	0	0	0
Upper respiratory tract infection (all forms)				
Pharyngitis	2	0	0	0
SYS ORGAN CLASS TOTAL:	7	0	0	0
Skin & subcutaneous tissue disorders				
Congenital skin anomalies				
Congenital nail disorder	3	0	0	0
Dermatitis & eczema				
Dermatitis NOS	2	0	0	0
Dermatitis lichenoid	1	0	0	0
Miscellaneous skin & subcutaneous tissue disorders				
Erythema nodosum	1	0	0	0
Pruritus	20	0	0	0
Photosensitivity eruptions				
Photosensitivity reaction	2	0	0	0
Rashes				
Localised skin reactions	1	0	0	0
Rash NOS	28	0	0	0
Rash erythematous	7	0	0	0
Rash maculo-papular	2	0	0	0
Vascular abnormalities of skin				
Purpura	2	0	0	0
Spider naevus	1	0	0	0
Angioedema				
Face oedema	5	0	0	0
Periorbital oedema	1	0	0	0
Urticaria				
Urticaria	16	0	0	0
Hair & hair follicle disorders				
Alopecia	2	0	0	0
Hair texture abnormal	1	0	0	0
Psoriasis & similar conditions				
Psoriasis	1	0	0	0
SYS ORGAN CLASS TOTAL:	96	0	0	0
TOTAL REACTIONS FOR DRUG:	512	1	0	0

TOTAL REPORTS: 339 TOTAL FATAL OUTCOME: 1

CHANGE OF LEGAL STATUS: FAMOTIDINE

Proposal

CSM has advised that famotidine should be excuded from POM for the short-term symptomatic relief of heartburn, dyspepsia and hyperacidity, subject to a maximum dose of 10mg, a maximum daily dose of 20mg and a maximum treatment period of 2 weeks.

Comment

[redacted] has noted that this is a very new drug to go from POM to P.

[redacted] has commented that whilst, like cimetidine, this is an H2 antagonist, it does not have the same effect on the liver, consequently its drug interaction profile is greatly reduced. They consider the proposal acceptable.

MCA response

Although newer than cimetidine or ranitidine, there is considerable prescription experience with this drug, which was first licensed in the UK in 1987 and is now registered in 65 countries; the first successful registration was in Japan in 1985.

In view of the safety data, the applicant estimates an overall marketed use of 18.8 million patients treated for 2.89 million patient years.

Recommendation

The Medicines Commission is asked to endorse the recommendation in MLX 198.

[redacted]

[redacted]

Medicines Control Agency
Department of Health
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Medical Department

[redacted]

Merck Sharp & Dohme Limited
Hertford Road
Hoddesdon
Hertfordshire EN11 9BU
Telephone Hoddesdon (0992) 467272
Cables Medome Hoddesdon
Telex 261915
Facsimile (0992) 451066

MERCK SHARP & DOHME

Our ref: JMS/CG/OCT93.113

22 October 1993

[redacted]
Medicines Inspectorate, Southern Region
G23, 3 East Grinstead House
London Road
EAST GRINSTEAD
West Sussex
RH19 1RR

Dear [redacted]

Provisional PL 0025/0312 PEPCID AC Film-coated Tablets 10 mg
Sites of Tablet Manufacture and Assembly

[redacted]

Yours sincerely

[redacted]

[redacted]

cc: [redacted] MCA, Market Towers

[redacted]

Medical Department

[redacted]

Merck Sharp & Dohme Limited
Hertford Road
Hoddesdon
Hertfordshire EN11 9BU
Telephone Hoddesdon (0992) 467272
Cables Medome Hoddesdon
Telex 261915
Facsimile (0992) 451066

CONFIRMATIO.

MERCK SHARP & DOHME

URGENT PANAFAX

Our ref: MG/NL/OCT93.22

21 October 1993

[redacted]
Business B: Abridged Licensing Business
Medicines Control Agency
Department of Health
Market Towers
1 Nine Elms Lane
Vauxhall
LONDON
SW8 5NQ

Dear [redacted]

RE: PEPCID AC Tablets PL 0025/0312-0313

Further to your telephone call of today, please find attached the UK sales figures for PEPCID Tablets (R), since launch. As you will see, the figures are provided on an annual basis from launch (1987), and also on a monthly basis for the past 3 years.

I hope this is the type of information that you are looking for. If you have any problems, please do not hesitate to contact me.

Regards.

Yours sincerely

[redacted]
Regulatory Affairs Department

Att

PEPCID Prescriptions

PRESCRIPTIONS (000's)

4 WEEK ENDING	ACTUAL	TREND
01.02.91	24.7	
01.03.91	24.8	
29.03.91	22.0	
26.04.91	19.4	
24.05.91	22.6	
21.06.91	24.3	
19.07.91	20.1	
16.08.91	20.3	
13.09.91	22.6	
11.10.91	23.8	
08.11.91	21.7	
06.12.91	22.6	
03.01.92	20.6	
	268.9	

PRESCRIPTIONS (000's)

4 WEEK ENDING	ACTUAL	TREND
31.01.92	23.0	23.0
28.02.92	20.8	20.8
27.03.92	20.5	20.5
24.04.92	21.9	21.9
22.05.92	22.8	22.8
19.06.92	21.4	21.4
17.07.92	19.7	19.7
14.08.92	19.1	19.1
11.09.92	17.1	17.1
09.10.92	19.9	19.9
06.11.92	16.8	16.8
04.12.92	20.6	20.6
01.01.93	16.9	16.9
	243.6	243.6

PRESCRIPTIONS (000's)

4 WEEK ENDING	ACTUAL	TREND
29.01.93	21.1	21.1
26.02.93	19.7	19.7
26.03.93	19.6	19.6
23.04.93	20.5	20.5
21.05.93	20.1	20.1
18.06.93	19.4	19.4
16.07.93	19.7	19.7
13.08.93	14.6	14.6
10.09.93		15.7
08.10.93		18.3
05.11.93		16.6
03.12.93		16.9
31.12.93		16.3
	154.7	238.5

PLN YTD
ACT YTD
ACH YTD

PEPCID Retail Purchases: Annual Breakdown

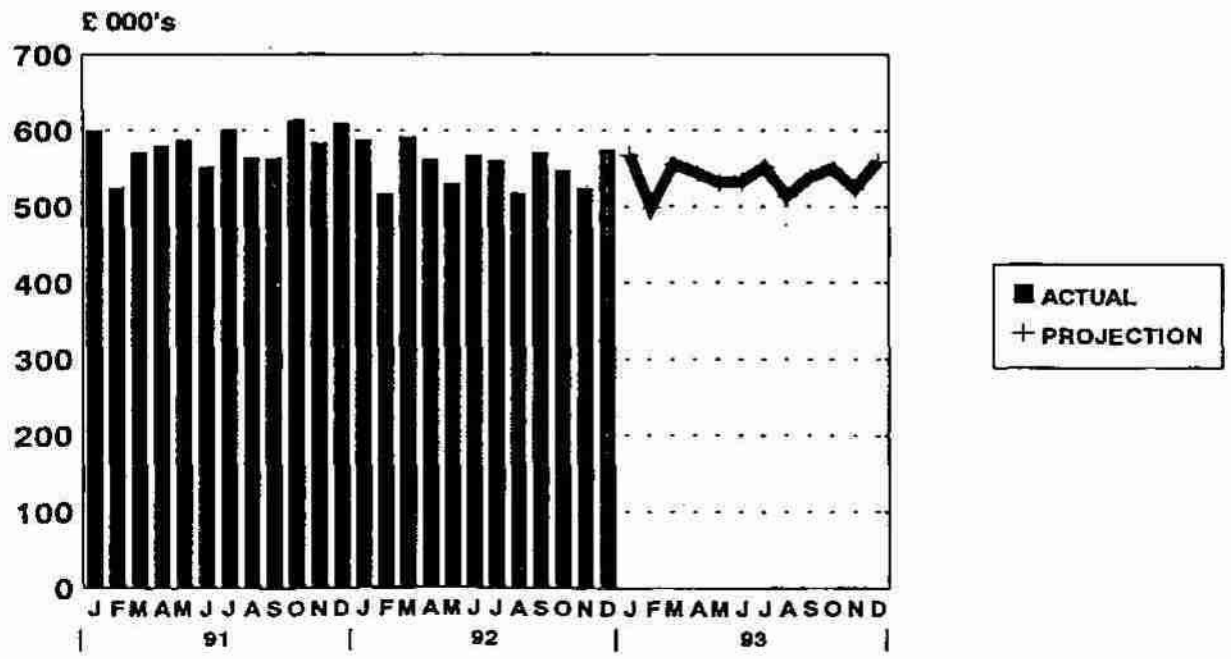
1987	1258*	)
1988	5609	)
1989	6123	)
1990	7066	) £,000's
1991	6975	)
1992	6678	)
1993 (MAT August)	6232	)

* Launched September 1987.

PEPCID RETAIL PURCHASES

	MONTHLY (£000's)	CUMULATIVE (£000's)		MONTHLY (£000's)	CUMULATIVE (£000's)
Jan 91	601.6	601.6	Jan 92	590.3	590.3
Feb 91	526.8	1128.4	Feb 92	519.6	1109.9
Mar 91	573.4	1701.8	Mar 92	594.3	1704.2
Apr 91	581.7	2283.5	Apr 92	564.2	2268.4
May 91	589.5	2873	May 92	531.9	2800.3
Jun 91	553.7	3426.7	Jun 92	569.9	3370.2
Jul 91	603.5	4030.2	Jul 92	563.2	3933.4
Aug 91	566.7	4596.9	Aug 92	519.9	4453.3
Sep 91	565.8	5162.7	Sep 92	572.4	5025.7
Oct 91	615.8	5778.5	Oct 92	550.1	5575.8
Nov 91	585.9	6364.4	Nov 92	525.6	6101.4
Dec 91	610.8	6975.2	Dec 92	576.2	6677.6

PEPCID RETAIL PURCHASES



SOURCE:BPI
U:\ULCMON\PEPRP

[redacted]

VALIDATION SHEET
MEDICINES CONTROL AGENCY ABRIDGED APPLICATIONS (NA)(01)(31/01/93)

2

NO. & CO. : PL 00025/0312
MERCK SHARP & DOHME LTD

DATE RECEIVED : 27/01/93
DATE REGISTERED : 27/01/93
DATE FEE PAID : 27/01/93
DATE NOTIFIED TO REG'N : 27/01/93
REC'D IN VALID'N : 29/01/93
VALIDATION DATE : 29/01/93

[redacted]

MANUFACTURER : F WOELM PHARMA GMBH, MAX-WOELM-STRASSE, 3440 ESCHWEGE, GERMANY.

MERCK SHARP & DOHME LTD, SHOTTON LANE, CRAMLINGTON, NORTHUMBERLAND NE 23 9JU

F MERCK SHARP & DOHME (ITALIA) SPA, VIA EMILIA 21,27100 PAVIA,ITALY

PRODUCT NAME : **BLOCAZIDE 10MG TABLETS (FILM-COATED)**

PHARMACEUTICAL FORM : FILM COATED TABLETS

PACK SIZE(S) : 2, 6, 10, 12, 18, 20, 30, 40, 50

LEGAL STATUS REQUESTED : PHARMACY SALE ONLY **METHOD OF SALE** : REGISTERED PHARMACIES

ACTIVE CONSTITUENTS : **FAMOTIDINE** USP 010.0 MG
F YAMANOUCHI IRELAND CO LTD DUBLIN EIRE
F YAMANOUCHI PHARM CO LTD TOKYO JAPAN

THERAPEUTIC CODE(S) : A30

DRUG SUBSTANCE DETAIL : USP SPECIFICATION. SEE PL 00025/0215-6 (g.8/9/87) Pepcid Tablets 20mg and 40mg.

CLINICAL USE : TREATMENT OF INDIGESTION, ACID INDIGESTION, NERVOUS INDIGESTION, HEARTBURN, DYSPEPSIA, ACIDITY, SYMPTOMS OF UPSET STOMACH ASSOCIATED WITH THESE CONDITIONS.

ROUTE OF ADMINISTRATION : ORAL

DOSAGE : ADULTS AND CHILDREN OVER 12 YEARS:- DOSAGE INTERVAL: AS NEEDED TO RELIEVE SYMPTOMS OR ONE HOUR BEFORE EATING FOR SYMPTOMS ASSOCIATED WITH FOOD AND BEVERAGE. MAXIMUM INTAKE IN 24 HOURS IS 20MG.

SUPPORTING DATA : MLA 201, EXPERT REPORTS. ABRIDGED CHEMISTRY & PHARMACY 2 VOL(S). TOX & PHARM DOC 1 VOL(S). CLINICAL DOC 13 VOL(S).

NOTES & BACKGROUND : 1. Application coming in with full data as a POM to P application for a 10mg film-coated tablet.

2. Applicant holds PL 00025/0215-6 (g.8/9/87) Pepcid Tablets 20mg and 40mg.

3. Records show that both AIM's have been used in previously granted licences.

INFORMATION SECTION : CONTACT INFORMATION ROOM ON ASSESSMENT.

OTHER INFORMATION : AAC

FEE : £17800
POM TO P
VALIDATOR [redacted]

SERIAL NUMBER : 81563

COMMITTEE DEADLINE : 30/05/93

MEDICAL ASSESSOR :

PHARMACEUTICAL ASSESSOR :

ROUTE :

[redacted]

H 1 / [redacted]

9. Description of essential processes in the manufacture:

FAMOTIDINE, MICROCRYSTALLINE CELLULOSE, AND PREGELATINISED MAIZE STARCH ARE GRANULATED WITH A WATER/ETHANOL MIXTURE, DRIED, MILLED, LUBRICATED WITH MAGNESIUM STEARATE AND TALC, AND COMPRESSED INTO TABLETS.

THE TABLET COATING SUSPENSION IS PREPARED BY DISPERSING THE METHYLHYDROXYPROPYL-CELLULOSE AND HYDROXYPROPYLCELLULOSE IN THE PURIFIED WATER AND THEN DISPERSING THE TITANIUM DIOXIDE, TALC AND RED IRON OXIDE IN THIS SOLUTION. THE SUSPENSION IS SPRAYED ON THE COMPRESSED TABLETS IN A STANDARD COATING PAN.

10. Finished Product Specification:

APPEARANCE:	*PALE-ROSE (PINK), ROUNDED-SQUARE, FILM-COATED TABLET WITH THE TRADEMARK PRINTED ON ONE SIDE.*
IDENTITY:	*CONFIRMED BY HPLC (OR ALTERNATIVE TLC METHOD).*
FAMOTIDINE ASSAY:	[redacted]
DEGRADATES:	[redacted]
UNIFORMITY OF CONTENT:	*MEETS THE EP/USP SPECIFICATION.*
DISSOLUTION:	[redacted]

Date: *24 JANUARY 1993*

[redacted]

G	1					/										

11. Arrangements for storage and address(es) of storage premises:

BULK TABLETS WILL BE STORED BRIEFLY AT THE SITE OF MANUFACTURE AND THE SITE OF ASSEMBLY. FINISHED PRODUCT WILL BE STORED BRIEFLY AT THE SITE OF ASSEMBLY, AND FOR DISTRIBUTION AT MSD, CRAMLINGTON, UK.

12. Special precautions for storage:

STORE BELOW 30°C; PROTECT FROM MOISTURE.

13. Nature of container and closure | Shelf-life (A) | Shelf-life (B) | Pack Size

Nature of container and closure	Shelf-life (A)	Shelf-life (B)	Pack Size
BLISTER PACKS WITH PVC BASE AND ALUMINIUM FOIL LIDDING.	*24 M*		*2*
			6
			10
			12
			18
			20

Unit

Notes: 1) Shelf-life should be expressed in months (M), weeks (W) or days (D) as appropriate eg 3 6 M
A = Unopened.
B = After reconstitution or when the container is opened for the first time, if appropriate.

2) The pack size should contain numbers only, right aligned. If a decimal point is required it should occupy one box.

3) Where applicable enter the unit of measure as MG, GM, ML, LT in the Unit box. No entry is required in the Unit box for solid dosage forms.

Date: *24 JANUARY 1993*

COMMERCIAL IN CONFIDENCE	**NUMBER:** PL 0025/0312
APPLICATION FOR A PRODUCT LICENCE:	**PRODUCT NAME:** Blocazide 10mg Film-coated Tablets
PROPOSED LICENCE HOLDER: Merck Sharp and Dohme Ltd Hertford Road Hoddesdon Herts EN11 9BU	**THERAPEUTIC CLASSIFICATION:** H_2-receptor antagonist **RECEIVED:** 27 January 1993 **MEETING:** May 1993
MANUFACTURER OF DOSAGE FORM: Woelm Pharma GMBH, Eschwege, Germany or MSD, Cramlington, Northumberland, UK or MSD (Italia), Pavia, Italy **LEGAL STATUS: P**	**COMMITTEE ON SAFETY OF MEDICINES** **SUB-COMMITTEE ON CHEMISTRY PHARMACY AND STANDARDS** **CONSIDERATION BY OTHER COMMITTEES:** **Sub-Committee onSafety and Efficacy** **Sub-Committee on Pharmacovigilance**
SALE/SUPPLY: Through registered pharmacies, under the supervision of a Pharmacist	**ASSESSED BY:** [redacted]

KEY WORDS

POM to P

SUMMARY

"POM" to "P" conversion of famotidine 10mg tablets, for the treatment of indigestion, acid indigestion, nervous indigestion, heartburn, dyspepsia, acidity and symptoms of upset stomach associated with these conditions.

No major pharmaceutical issues.

[redacted]

A 1 / [ ]

[ ] [ ] [ ]

Form MLA 201

PRODUCT PARTICULARS - a complete set of pages should be included for each strength of product

PL Number of Product: (Official use only)

[ ] [ ] [ ] [ ] [ ] / [ ] [ ] [ ] [ ] [ ]

1. Name of Product and Strength: *BLOCAZIDE 10 MG*

(Official use only) [ ]

[ ] [ ] [ ]

[ ] [ ] [ ]

[ ] [ ] [ ]

2. Full description of Pharmaceutical form (eg tablets, slow-release tablets, capsules etc):

FILM-COATED TABLET FOR ORAL ADMINISTRATION TO HUMAN BEINGS.

(Official use only) [ ] [ ]

[ ] [ ] [ ] [ ]

[ ] [ ] [ ] [ ]

[ ] [ ] [ ] [ ]

3a. Legal status requested (please tick in appropriate box) (Official use only) [ ]

Prescription		Pharmacy	X	General Sales		Not Applicable	

3b. Method of retail sale or supply: *FOR SUPPLY TO MEMBERS OF THE GENERAL PUBLIC THROUGH REGISTERED PHARMACIES, UNDER THE SUPERVISION OF A PHARMACIST.*

(Official use only) [ ]

Text should be completed in block capitals

Date: *24 JANUARY 1993*

(Official Use Only)

0	1						/											

4. Active Constituents

(Official use only)	Name	Specification Reference			Quantity/Dose Unit or % quantity					Unit	
	FAMOTIDINE	*U*	*S*	*P*		*1*	*0 • 0*			*M*	*G*
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				

Details of any overages:- these should not be included in the Formulation Columns but stated in this section.

*) Please enter constituent(s) as actual substances included in the formulation, eg. as salt and then as base equivalent where applicable.

2) See page E1, paragraph 2 for approved abbreviations

Where a Specification does not refer to the latest published monograph, the relevant year should be included in the Name Column and set in the Specification Reference Column. Where an ingredient has no official monograph please enter HSE in the Specification Reference Column.

3) In the case of liquid preparations: all quantities for oral preparations should relate to a 5 ml dosage. Please state in dosage information any deviation from this rule. Quantity should be expressed as a percentage for other liquid preparations, including parenterals please insert WW, WV etc as appropriate in the Unit Column. DO NOT INSERT a percentage sign, this is automatically inserted by computer.

4) The following abbreviations for units are recommended:-
NG nanogrammes; UG microgrammes; MG milligrammes; GM grammes; KG kilogrammes; UL microlitres; ML millilitres; L litres; U units (u); KU kilounits (1,000 u); MU megaunits (1,000,000 u); I.U. international units; UC microcuries; BC becquerels.

) Trailing zeros following the decimal point may be omitted eg. 10.02 mg will suffice.

6) Please photocopy page if more space for constituents is required.

Date: *24 JANUARY 1993*

C 1 / [redacted]

5. Recommended clinical indications and route(s) of administration

TREATMENT OF:

- *INDIGESTION*
- *ACID INDIGESTION*
- *NERVOUS INDIGESTION*
- *HEARTBURN*
- *DYSPEPSIA*
- *ACIDITY*
- *SYMPTOMS OF UPSET STOMACH ASSOCIATED WITH THESE CONDITIONS*

ROUTE OF ADMINISTRATION: ORAL

(Official use only)

All entries must be made in full. Cross references, eg. to accompanying data sheets are not acceptable.

Date: *24 JANUARY 1993*

[redacted]

B 1 / [ ]

6. Recommended doses and dosage schedules:

Distinguish between adults, children and the elderly and between different clinical indications

[ ] (Official Use Only)

ADULTS AND CHILDREN 12 YEARS OF AGE OR OLDER:
DOSAGE: 10 MG.

DOSAGE INTERVAL: AS NEEDED TO RELIEVE SYMPTOMS OR ONE HOUR BEFORE EATING FOR SYMPTOMS ASSOCIATED WITH FOOD AND BEVERAGE.

MAXIMUM INTAKE IN 24 HOURS: 20 MG.

NO DOSAGE ADJUSTMENT IS NECESSARY FOR THE ELDERLY.

(Official use only)

Date: *24 JANUARY 1993*

[redacted]

B 2 / [redacted]

7. Contraindications, Precautions and Warnings listed, with titles. In the following order:-

a) Contraindications
b) Interactions with other medicaments and other forms of interaction
c) Effects on ability to drive and to use machines
d) Other undesirable effects (frequency and seriousness)
e) Use in pregnancy and lactation
f) Other special warnings and precautions
g) Overdose (symptoms, emergency procedures, antidotes)
h) Incompatibilities (major)

A) *CONTRAINDICATIONS*

HYPERSENSITIVITY TO ANY COMPONENT OF THIS PRODUCT.

B) *INTERACTIONS WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION*

NO DRUG INTERACTIONS OF CLINICAL IMPORTANCE HAVE BEEN IDENTIFIED. 'BLOCAZIDE' DOES NOT INTERACT WITH THE CYTOCHROME P450-LINKED DRUG METABOLIZING ENZYME SYSTEM. COMPOUNDS METABOLIZED BY THIS SYSTEM WHICH HAVE BEEN TESTED IN MAN HAVE INCLUDED WARFARIN, THEOPHYLLINE, PHENYTOIN, DIAZEPAM, PROPRANOLOL, AMINOPYRINE AND ANTIPYRINE. INDOCYANINE GREEN AS AN INDEX OF HEPATIC BLOOD FLOW AND/OR HEPATIC DRUG EXTRACTION HAS BEEN TESTED AND NO SIGNIFICANT EFFECTS HAVE BEEN FOUND.

CONCOMITANT USE OF ALUMINIUM HYDROXIDE/MAGNESIUM HYDROXIDE DOES NOT INFLUENCE THE PHARMACODYNAMICS OR BIOAVAILABILITY OF 'BLOCAZIDE'.

'BLOCAZIDE' DOES NOT AFFECT BLOOD ALCOHOL LEVELS FOLLOWING ORAL INGESTION OF ETHANOL.

C) *EFFECTS ON ABILITY TO DRIVE AND OPERATE MACHINERY*

NONE KNOWN.

D) *OTHER UNDESIRABLE EFFECTS (FREQUENCY AND SERIOUSNESS)*

'BLOCAZIDE' HAS BEEN DEMONSTRATED TO BE GENERALLY WELL-TOLERATED. SIDE EFFECTS REPORTED IN ≥1% OF PATIENTS WERE HEADACHE AND DIZZINESS. THESE OCCURRED WITH COMPARABLE FREQUENCY IN PATIENTS TREATED WITH PLACEBO.

E) *USE IN PREGNANCY AND LACTATION*

CLINICAL TRIALS IN PREGNANT WOMEN HAVE NOT BEEN PERFORMED. AS WITH MOST MEDICINES, 'BLOCAZIDE' IS NOT RECOMMENDED FOR USE IN PREGNANCY, AND SHOULD BE USED ONLY UNDER THE ADVICE OF A PHYSICIAN.

FAMOTIDINE IS DETECTABLE IN HUMAN MILK. NURSING MOTHERS SHOULD NOT TAKE THIS DRUG OR SHOULD STOP NURSING.

(Official use only)

Date: *24 JANUARY 1993*

[redacted]

B 2 / [redacted]

7. Contraindications, Precautions and Warnings listed, with titles. In the following order:-

a) Contraindications
b) Interactions with other medicaments and other forms of interaction
c) Effects on ability to drive and to use machines
d) Other undesirable effects (frequency and seriousness)
e) Use in pregnancy and lactation
f) Other special warnings and precautions
g) Overdose (symptoms, emergency procedures, antidotes)
h) Incompatibilities (major)

E) *USE IN PREGNANCY AND LACTATION (CONTINUED)*

REPRODUCTIVE STUDIES HAVE BEEN PERFORMED IN RATS AND RABBITS AT ORAL DOSES OF UP TO 2000 AND 500 MG/KG/DAY, RESPECTIVELY (APPROXIMATELY 5000 AND 1250 TIMES THE MAXIMUM RECOMMENDED HUMAN DOSE, RESPECTIVELY), AND HAVE REVEALED NO EVIDENCE OF IMPAIRED FERTILITY OR HARM TO THE FETUS DUE TO FAMOTIDINE.

IN STUDIES WITH RATS GIVEN ORAL DOSES OF UP TO 2000 MG/KG/DAY OR INTRAVENOUS DOSES OF 200 MG/KG/DAY (APPROXIMATELY 5000 AND 500 TIMES THE MAXIMUM RECOMMENDED HUMAN DOSE, RESPECTIVELY), FERTILITY AND REPRODUCTIVE PERFORMANCE WERE NOT AFFECTED.

F) *OTHER SPECIAL WARNINGS AND PRECAUTIONS*

IN CLINICAL TRIALS, PATIENTS WITH OTHER UNDERLYING ACID GASTROINTESTINAL DISEASES (EG, DUODENAL ULCER, GASTRIC ULCER) DID NOT EXPERIENCE COMPLICATIONS; IN GENERAL, THEY DID NOT EXHIBIT A CLINICALLY SIGNIFICANT DETERIORATION IN THEIR CONDITION. HOWEVER, IF PATIENTS HAVE DIFFICULTY SWALLOWING OR ABDOMINAL DISCOMFORT PERSISTS THE UNDERLYING CAUSE SHOULD BE DETERMINED.

THERAPY SHOULD NOT EXCEED TWO WEEKS WITHOUT MEDICAL CONSULTATION.

WHEN 'BLOCAZIDE' WAS ADMINISTERED TO ELDERLY PATIENTS IN CLINICAL TRIALS, NO INCREASE IN THE INCIDENCE OR CHANGE IN THE TYPE OF DRUG-RELATED SIDE EFFECTS WAS OBSERVED.

G) *OVERDOSE*

PATIENTS HAVE TOLERATED DOSES UP TO 800 MG/DAY FOR MORE THAN A YEAR WITHOUT DEVELOPMENT OF SIGNIFICANT SIDE EFFECTS.

H) *INCOMPATIBILITIES*

NONE.

(Official use only)

Date: *24 JANUARY 1993*

[redacted]

E 1 / [redacted]

8. Other Constituents

(Official use only)	Name	Specification Reference			mod	Quantity/Dose Unit or % quantity	Unit	
	TABLET CORE:				[redacted]	[redacted]		
	MAGNESIUM STEARATE	*E*	*P*				*M*	*G*
	MICROCRYSTALLINE CELLULOSE	*E*	*P*				*M*	*G*
	PREGELATINISED MAIZE STARCH	*B*	*P*				*M*	*G*
	TALC	*E*	*P*				*M*	*G*
	INDUSTRIAL METHYLATED SPIRIT (OR ALCOHOL 95%	*B* *U*	*P* *S*	*P)*				
	PURIFIED WATER	*E*	*P*					
	TABLET COAT:							
	HYDROXYPROPYL-CELLULOSE	*E*	*P*				*M*	*G*
	METHYLHYDROXY-PROPYLCELLULOSE	*E*	*P*				*M*	*G*
	RED IRON OXIDE E172	*E*	*E*	*C*			*M*	*G*
	TALC	*E*	*P*				*M*	*G*
	TITANIUM DIOXIDE E171	*E*	*P*				*M*	*G*
	PURIFIED WATER	*E*	*P*					

1) Please leave a line between different components of the dosage form, eg. for capsule shell components, coating components.
2) Where a specification reference does not refer to the latest published monograph, the relevant year should be included in the Name Column and not in the Specification Reference Column. Where an ingredient has no official monograph please enter HSE in the Specification Reference Column. Abbreviations to be used for specification are:- BP, EP, BPC, BNF, USP, NF, FRP, DAB, IP, NDP, JAP, PHV, BHP.
3) Please complete modifier column marked MOD as follows:
Insert TO if final volume cannot be expressed as a complete quantity.
Insert ND for substances not detectable in the final formulation, eg. solvents.
Insert QS if quantity not fixed eg. for substances used to adjust pH.
4) Recommended abbreviations for units are given on page D1, paragraph 4.
5) In the case of liquid preparations: all quantities for oral preparations should relate to a 5 ml dosage. Please state in dosage information any deviation from this rule. Quantity should be expressed as a percentage for other liquid preparations, including parenterals please insert WW, WV etc as appropriate in the Unit Column. DO NOT INSERT a percentage sign, this is automatically inserted by computer.
6) Trailing zero's following the decimal point may be omitted eg. 10.02 mg will suffice.
7) Please photocopy page if more space for constituents is required.

Date: *24 JANUARY 1993*

[redacted]

H 1 / [redacted]

9. Description of essential processes in the manufacture:

FAMOTIDINE, MICROCRYSTALLINE CELLULOSE, AND PREGELATINISED MAIZE STARCH ARE GRANULATED WITH A WATER/ETHANOL MIXTURE, DRIED, MILLED, LUBRICATED WITH MAGNESIUM STEARATE AND TALC, AND COMPRESSED INTO TABLETS.

THE TABLET COATING SUSPENSION IS PREPARED BY DISPERSING THE METHYLHYDROXYPROPYL-CELLULOSE AND HYDROXYPROPYLCELLULOSE IN THE PURIFIED WATER AND THEN DISPERSING THE TITANIUM DIOXIDE, TALC AND RED IRON OXIDE IN THIS SOLUTION. THE SUSPENSION IS SPRAYED ON THE COMPRESSED TABLETS IN A STANDARD COATING PAN.

10. Finished Product Specification:

APPEARANCE:	*PALE-ROSE (PINK), ROUNDED-SQUARE, FILM-COATED TABLET WITH THE TRADEMARK PRINTED ON ONE SIDE.*
IDENTITY:	*CONFIRMED BY HPLC (OR ALTERNATIVE TLC METHOD).*
FAMOTIDINE ASSAY:	[redacted]
DEGRADATES:	[redacted]
UNIFORMITY OF CONTENT:	*MEETS THE EP/USP SPECIFICATION.*
DISSOLUTION:	*A MINIMUM OF 85% OF THE LABEL CLAIM DISSOLVED IN 30 MINUTES.*

Date: *24 JANUARY 1993*

[redacted]

G 1 [ ][ ][ ][ ][ ][/][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

11. Arrangements for storage and address(es) of storage premises:

BULK TABLETS WILL BE STORED BRIEFLY AT THE SITE OF MANUFACTURE AND THE SITE OF ASSEMBLY. FINISHED PRODUCT WILL BE STORED BRIEFLY AT THE SITE OF ASSEMBLY, AND FOR DISTRIBUTION AT MSD, CRAMLINGTON, UK.

12. Special precautions for storage:

STORE BELOW 30°C; PROTECT FROM MOISTURE.

13. Nature of container and closure | Shelf-life (A) | Shelf-life (B) | Pack Size

Nature of container and closure	Shelf-life (A)	Shelf-life (B)	Pack Size
OPAQUE HDPE BOTTLES WITH LDPE CLOSURES.	*24M*		*30*
			40
			50

Unit

Notes: 1) Shelf-life should be expressed in months (M), weeks (W) or days (D) as appropriate eg 3 6 M
A = Unopened.
B = After reconstitution or when the container is opened for the first time, if appropriate.

2) The pack size should contain numbers only, right aligned. If a decimal point is required it should occupy one box.

3) Where applicable enter the unit of measure as MG, GM, ML, LT in the Unit box. No entry is required in the Unit box for solid dosage forms.

Date: *24 JANUARY 1993*

[redacted]

G 1 [ ][ ][ ][ ][ ][/][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

11. Arrangements for storage and address(es) of storage premises:

BULK TABLETS WILL BE STORED BRIEFLY AT THE SITE OF MANUFACTURE AND THE SITE OF ASSEMBLY. FINISHED PRODUCT WILL BE STORED BRIEFLY AT THE SITE OF ASSEMBLY, AND FOR DISTRIBUTION AT MSD, CRAMLINGTON, UK.

12. Special precautions for storage:

STORE BELOW 30°C; PROTECT FROM MOISTURE.

13. Nature of container and closure | Shelf-life (A) | Shelf-life (B) | Pack Size

Nature of container and closure	Shelf-life (A)	Shelf-life (B)	Pack Size
BLISTER PACKS WITH PVC BASE AND ALUMINIUM FOIL LIDDING.	*24M*		*2*
			6
			10
			12
			18
			20

Unit

Notes: 1) Shelf-life should be expressed in months (M), weeks (W) or days (D) as appropriate eg 3 6 M
A = Unopened.
B = After reconstitution or when the container is opened for the first time, if appropriate.

2) The pack size should contain numbers only, right aligned. If a decimal point is required it should occupy one box.

3) Where applicable enter the unit of measure as MG, GM, ML, LT in the Unit box. No entry is required in the Unit box for solid dosage forms.

Date: *24 JANUARY 1993*

[redacted]

K | 1 | | | | | | / | | | | | | | | | |

14. Pharmacological particulars:

'BLOCAZIDE' IS A POTENT COMPETITIVE H_2-RECEPTOR ANTAGONIST.

'BLOCAZIDE' HAS A RAPID ONSET OF ACTION FOLLOWING ORAL ADMINISTRATION AND, AT THE RECOMMENDED DOSES, 'BLOCAZIDE' HAS A LONG DURATION OF ACTION AND IS HIGHLY EFFECTIVE AT RELATIVELY LOW BLOOD CONCENTRATIONS. DURATION OF ACTION, PLASMA CONCENTRATION, AND URINARY RECOVERY ARE DOSE-RELATED.

'BLOCAZIDE' REDUCES THE ACID AND PEPSIN CONTENT, AS WELL AS THE VOLUME, OF BASAL, NOCTURNAL, AND STIMULATED GASTRIC SECRETION.

IN CLINICAL TRIALS 'BLOCAZIDE' PROVIDED RAPID SYMPTOM RELIEF. WHEN ADMINISTERED BEFORE A TEST MEAL, FAMOTIDINE REDUCED SYMPTOMS THAT WOULD OTHERWISE HAVE BEEN EXPECTED.

AFTER ORAL ADMINISTRATION, A DOSE-RESPONSE RELATIONSHIP WAS CLEARLY DEMONSTRATED FROM 0.5 AND 10 MG FAMOTIDINE IN TERMS OF RAISING GASTRIC PH BETWEEN AND AFTER MEALS. FAMOTIDINE DOSES OF 2.5 TO 10 MG WERE DEMONSTRATED TO PRODUCE A STATISTICALLY SIGNIFICANT EFFECT OF GASTRIC PH AS COMPARED TO PLACEBO. THE ONSET OF EFFECT FOR THE 5 AND 10 MG DOSES WERE SEEN AT APPROXIMATELY 1.5 HOURS POSTDOSE WHILE THAT OF THE 2.5 MG DOSE WAS NOT SEEN UNTIL 2.5 HOURS POSTDOSE. THE MAXIMUM EFFECT, AS MEASURED BY PEAK MEAN PH VALUE, OCCURRED AT 3.5 HOURS. THE ACTIVITY OF THE 5 AND 10 MG DOSES CONTINUED UNTIL APPROXIMATELY 9 HOURS POSTDOSE. FAMOTIDINE IS WELL-TOLERATED AT THESE DOSE LEVELS.

SYSTEMIC EFFECTS OF 'BLOCAZIDE' IN THE CNS, CARDIOVASCULAR, RESPIRATORY OR ENDOCRINE SYSTEMS WERE NOT NOTED IN CLINICAL PHARMACOLOGY STUDIES. ALSO, NO ANTI-ANDROGENIC EFFECTS WERE NOTED IN CLINICAL PHARMACOLOGY STUDIES. SERUM HORMONE LEVELS, INCLUDING PROLACTIN, CORTISOL, THYROXINE (T_4), AND TESTOSTERONE, WERE NOT ALTERED AFTER TREATMENT WITH 'BLOCAZIDE'.

15. Pharmacokinetic particulars:

'BLOCAZIDE' OBEYS LINEAR KINETICS.

IN PHARMACOKINETIC STUDIES IN THE ELDERLY, NO CLINICALLY SIGNIFICANT AGE-RELATED CHANGES WERE DETECTED.

COMPARED TO HISTORICAL DATA FROM YOUNGER SUBJECTS, AGE DOES NOT APPEAR TO AFFECT THE BIOAVAILABILITY OF SINGLE DOSES OF FAMOTIDINE; HOWEVER, THE ELIMINATION APPEARS TO BE REDUCED IN ELDERLY SUBJECTS COMPARED WITH YOUNGER SUBJECTS.

'BLOCAZIDE' IS RAPIDLY ABSORBED WITH DOSE-RELATED PEAK PLASMA CONCENTRATIONS OCCURRING AT 1-3 HOURS. THE MEAN BIOAVAILABILITY OF AN ORAL DOSE IS 40-45%. BIOAVAILABILITY IS NOT CLINICALLY AFFECTED BY THE PRESENCE OF FOOD IN THE STOMACH. 'BLOCAZIDE' UNDERGOES MINIMAL FIRST-PASS METABOLISM. REPEATED DOSES DO NOT LEAD TO ACCUMULATION OF THE DRUG.

PROTEIN BINDING IN THE PLASMA IS RELATIVELY LOW (15-20%). THE PLASMA HALF-LIFE AFTER A SINGLE ORAL DOSE OR MULTIPLE REPEATED DOSES (FOR 5 DAYS) WAS APPROXIMATELY 3 HOURS.

METABOLISM OF THE DRUG OCCURS IN THE LIVER, WITH FORMATION OF THE INACTIVE SULPHOXIDE METABOLITE.

FOLLOWING ORAL ADMINISTRATION, THE MEAN URINARY EXCRETION OF THE ABSORBED DOSE OF FAMOTIDINE IS 65-70%. OF THE TOTAL ORAL DOSE ADMINISTERED, 25-30% IS RECOVERED AS UNCHANGED COMPOUND IN THE URINE. RENAL CLEARANCE IS 250-450 ML/MIN, INDICATING SOME TUBULAR EXCRETION. A SMALL AMOUNT MAY BE EXCRETED AS THE SULPHOXIDE.

A 10 MG CHEWABLE TABLET 'BLOCAZIDE' WAS FOUND TO BE BIOEQUIVALENT TO A 10 MG FILM-COATED TABLET 'BLOCAZIDE'.

Date: 24 JANUARY 1993

[redacted]

L 1 / [ ]

16. Name(s) of manufacturers and site(s) of manufacture of (a) the active substance(s) and (b) the dosage form

(a) The active substance(s)

YAMANOUCHI IRELAND CO LTD
DAMASTOWN, MULHADDART
DUBLIN 15
IRELAND

OR

(CONTINGENT SOURCE)
YAMANOUCHI PHARMACEUTICAL CO LTD
NO. 1-8, AZUSAWAL-CHOME
ITABASHI-KU, TOKYO, 174, JAPAN

(b) The dosage form

WOELM PHARMA GMBH
MAX-WOELM-STRASSE, 3440 ESCHWEGE
GERMANY

OR

MERCK MANUFACTURING DIVISION
MERCK SHARP & DOHME LIMITED
SHOTTON LANE, CRAMLINGTON
NORTHUMBERLAND, NE23 9JU

OR

MERCK MANUFACTURING DIVISION
MERCK SHARP & DOHME (ITALIA) SPA
VIA EMILIA 21, 27100 PAVIA
ITALY

17. Assembler(s):

BLISTER PACKS

AS THE MANUFACTURERS OF THE DOSAGE FORM

BOTTLE PACKS

MERCK MANUFACTURING DIVISION
MERCK SHARP & DOHME BV
WAARDERWEG 39, HAARLEM, NETHERLANDS

18. Importer:

MERCK MANUFACTURING DIVISION
MERCK SHARP & DOHME LIMITED
SHOTTON LANE
CRAMLINGTON
NORTHUMBERLAND
NE23 9JU

19. Site and arrangements for quality control:

FULL QUALITY CONTROL TESTING WILL BE PERFORMED AT THE SITE OF MANUFACTURE. IMPORTED MATERIAL WILL BE ACCOMPANIED BY ANALYTICAL PROTOCOLS; IDENTITY TESTING WILL BE CARRIED OUT ON IMPORTED MATERIAL AT MSD, CRAMLINGTON.

20. Distributor (where applicable)

MERCK SHARP & DOHME LIMITED, CRAMLINGTON.

21. List other countries of registration:

FAMOTIDINE TABLETS, 20 AND 40 MG ARE REGISTERED IN MOST COUNTRIES WORLDWIDE FOR PRESCRIPTION USE. APPLICATION FOR OVER-THE-COUNTER USE OF THE 10 MG STRENGTH TABLET WILL BE MADE IN A NUMBER OF COUNTRIES E.G. AUSTRIA, BELGIUM, DENMARK, FRANCE, SWITZERLAND, SWEDEN, USA ETC.

Date: *24 JANUARY 1993*

[redacted]

AEB/PAF/SP/BLOCAZID

ABRIDGED PRODUCT LICENCE APPLICATION

ASSESSMENT REPORT

LICENCE NUMBER:	PL 0025/0312
PROPRIETARY NAME:	Blocazide 10mg Film-coated Tablets
ACTIVE CONSTITUENT:	Famotidine 10mg
COMPANY NAME:	Merck Sharp and Dohme Limited
LEGAL STATUS:	Pharmacy Medicine Requested.

1. BACKGROUND

This product licence application proposes to make famotidine 10mg tablets available as a Pharmacy Medicine. The proposed indications are the treatment of indigestion, acid indigestion, nervous indigestion, heartburn, dyspepsia, acidity and symptoms of upset stomach associated with these conditions. The dosage for adults and children of 12 years and over is over is one tablet as needed to relieve symptoms, or one hour before eating for symptoms associated with food and beverage. The maximum daily dose is 20mg with a maximum therapy period of two weeks without medical consultation.

Merck Sharp and Dohme (MS&D) are the originator of famotidine in the UK, through a licensing agreement with Yamanouchi of Japan. MS&D hold product licences for, and market, Pepcid Tablets 20mg and 40mg, PL 0025/0215-6, granted 8.9.87. An application is pending for Pepcid IV Injection 20mg/vial.

No product licences have been granted to date for H_2-receptor antagonists to be sold as Pharmacy Medicines. An application from Beecham Group plc for Dyspel Tablets (cimetidine 100mg) was considered by the CSM in December 1992. The company declined to accept the conditions on which the grant of a licence was recommended (restricting use to the prophylactic management of nocturnal heartburn) and an appeal is pending.

SUMMARY

Proposal to make famotidine 10mg tablets available as a Pharmacy Medicine for the treatment of indigestion, acid indigestion, nervous indigestion, heartburn, dyspepsia, acidity and symptoms of upset stomach associated with these conditions.

No major pharmaceutical quality problems.

[redacted]

2. PHARMACEUTICAL ASSESSMENT REPORT

2.1 Drug Substance - Famotidine

MS&D are the originator of famotidine in the UK, and the proposed specification for famotidine (polymorph I) is identical to that applied in the marketed Pepcid Tablets 20mg and 40mg.

2.2 Dosage Form

Formulation and Manufacture

Satisfactory specifications have been provided for each excipient in the conventional film-coated formulation. The formulation is qualitatively the same as that of Pepcid Tablets 20mg and 40mg, although the three strengths are not in scale to each other. Comprehensive pharmaceutical development data have been provided. Accelerated stability studies used for container selection, and the effects of scale-up have been reported. Some conversion from polymorph I to polymorph II may occur during granulation and compression. This may be considered acceptable since the two forms have previously been demonstrated to be bioequivalent.

Capsule shaped tablets were used in some of the clinical studies. These have been shown to have the same in-vitro dissolution profile as the rounded-shaped tablets proposed for marketing. A formulation differing only in film coat colour was also used in some trials. The colour difference is unlikely to effect bioavailability.

The manufacturing process is conventional with satisfactory in-process controls applied to the moisture content of the dried granulate [redacted] and the uncoated tablets. The company state that process validation will be performed on the initial production batches and that batch data to date indicate a satisfactory uniform product. This may be acceptable for a product closely related to the marketed Pepcid 20mg and 40mg formulations and manufactured using the same process. However, all production to date has been at MS&D, West Point, Pennsylvania, USA - not one of the facilities proposed for routine manufacture (see MLA 201, page 11). Process validation protocols should be provided for dosage form manufacture at each of the proposed sites.

[redacted]

Finished Product Specification

The range of tests and limits applied are based upon those applied to Pepcid Tablets 20mg and 40mg and upon the USP monograph for Famotidine Tablets. Blocazide Tablets comply with the USP monograph. Satisfactory, detailed, analytical validation data have been provided for the reverse phase HPLC active/related substances assay and the dissolution test assay.

The inclusion of a related substances test is an addition to the specifications registered for the higher strength tablets. The limits proposed are:

[redacted]

The individual impurity limits reflect stability data and the total limit is the sum of the maximum levels of the individuals. The limits may be considered acceptable.

The dissolution test procedure (USP paddle 50rpm, 900ml 0.1M phosphate buffer pH 4.5 at 37°C) is that of the Famotidine tablets USP monograph and is currently used for Pepcid tablets 20mg and 40mg. A satisfactory limit ($\leq$ 85% 30 min) is applied.

Stability studies indicate that the product is hygroscopic. A test for moisture content, together with a suitable limit, should be included.

Three satisfactory batch analyses [redacted] have been provided from manufacture at MS&D, West Point, Pennsylvania, USA.

Stability

One of the proposed packs is an HPDE bottle for which both child resistant and non-child resistant closures are proposed. The use of non-child resistant closures is undesirable and no justification has been provided for their inclusion.

Satisfactory data from three batches stored in both packs for 18 months at 30°C have been submitted in support of a proposed shelf-life of 24 months stored below 30° and protected from moisture. The blister pack data report a very slight moisture uptake. Short term data from elevated temperature and humidity conditions have been submitted. Supportive data from early development batches (36 months) and the marketed 20mg and 40mg products (50 months) has also been included.

[redacted]

Bioavailability

An in-vivo study to demonstrate bioequivalence across the range of tablets strengths, i.e. between Blocazide tablets 10mg, Pepcid tablets 20mg and 40mg, has not been provided.

The tablet core formulations are similar (quantities in mg):

	Blocazide 10mg	Pepcid 20mg	Pepcid 40mg
Famotidine Magnesium Stearate Microcrystalline cellulose Pregelatinised Maize Starch Talc IMS and Purified Water	[redacted]		

The film coats also differ only slightly.

In-vivo bioequivalence between Pepcid tablets 20mg and 40mg was demonstrated in the 1987 product licence application. The formulation differences between Blocazide 10mg and Pepcid 20mg are similar to those between Pepcid 20mg and 40mg. Satisfactory comparative in-vitro dissolution data may therefore be considered satisfactory to demonstrate equivalence across the range of tablets strengths.

Data to compare the in-vitro dissolution profile of Blocazide 10mg film-coated tablets with that of Pepcid tablets 20mg and 40mg should be provided.

Product Name

The opinion of the Committee is sought on the suitability of the name Blocazide. It may infer, to health professionals, a combination of Blocadren (timolol maleate - MS&D) and hydrochlorothiazide. However Blocazide is to be marketed direct to the consumer, who is unlikely to make such an assumption.

Legal Status Change

Self-medication of the proposed indications is common, often using antacids. Famotidine 10mg tablets may be considered a suitable addition to the Pharmacists armamentarium.

3. PHARMACEUTICAL RECOMMENDATION

A product licence for this product should be granted subject to the outstanding points being resolved.

[redacted]

March 1993

[redacted]

3. PRE-CLINICAL ASSESSMENT REPORT

Blocazide Tablets contain famotidine as active substance, one of the class of histamine antagonists acting specifically at H_2 receptor sites.

In this application to change the legal status, there is no new preclinical (or non-clinical) data. The existing preclinical safety base is summarised and commented upon in an abbreviated Expert Report (Appendix I).

The conclusion is that nothing in this preclinical database raises concerns about the proposed change to self-medication. A full range of animal studies was undertaken and reported in support of the original PL application and these remain relevant and appropriate to allow the less-controlled use under P status. There are thus no preclinical reasons to oppose the grant of a change in legal status from POM to P for Blocazide 10mg Tablet formulations.

4. MEDICAL ASSESSMENT REPORT

[redacted]

4.1 Indications

"Treatment of indigestion, acid indigestion, nervous indigestion, heart burn, dyspepsia, acidity and symptoms of upset stomach associated with these conditions".

The use of Blocazide in these indications is in respect of short term treatment on an "as required" basis. Treatment should not exceed two weeks without medical consultation.

4.2 Dose and Dosage Schedule

"Adults and Children 12 years of age or older:
Dosage: 10mg.

Dosage Interval: as needed to relieve symptoms or one hour before eating for symptoms associated with food and beverage.

Maximum intake in 24 hours: 20mg.

No dosage adjustment is necessary for the elderly".

Administration is via the oral route.

The applicant is seeking Pharmacy Status and intends that Blocazide should only be used as a non-prescription medication for a maximum period of two weeks. This must be clearly stated in the licence documentation under Dosage Schedules (currently the statement is made to this effect on page 6a, 7f under the heading "Other Special Warnings and Precautions"). The maximum treatment period of two weeks must also be clearly stated in the patient information and on the product labelling.

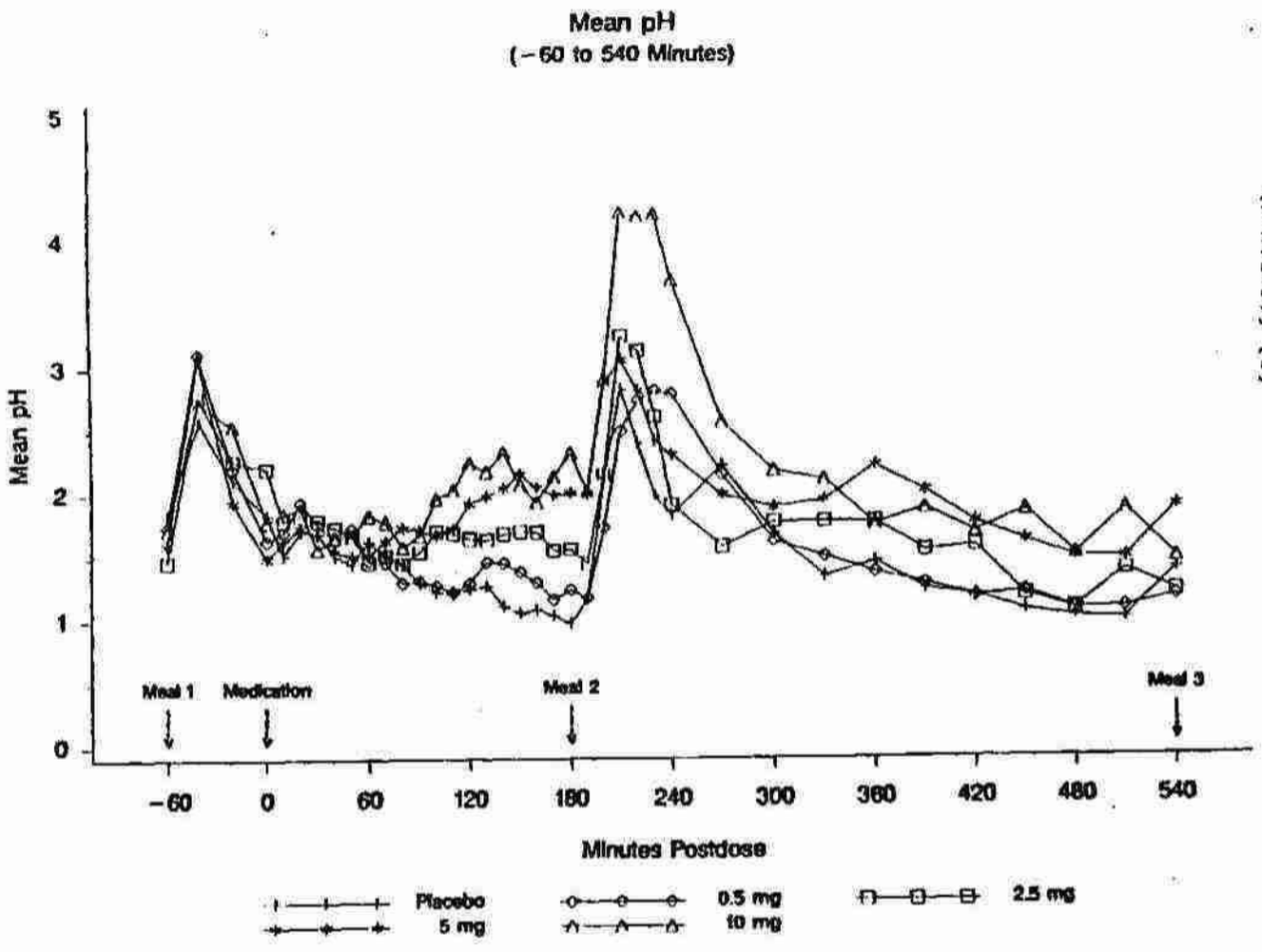
[redacted]

4.3 **Clinical Pharmacology** - see Appendix II for Study summaries.

Pharmacodynamics

The pharmacodynamics of famotidine were fully evaluated in the original product licence application (PL 0025/0215-6) and therefore this application confines itself primarily to the effects of famotidine on gastric acid secretion.

A dose ranging study in 10 male volunteers, to assess a range of doses of famotidine from 0.5mg to 10mg (film-coated tablets) is presented. The study was placebo controlled and the doses have been assessed against between meal (high protein) and meal stimulated acidity using an intragastric pH probe and analysing continuous intragastric pH.



Mean Intragastric pH Response Before and Following Famotidine [-60 Minutes (-1 Hour) to 540 Minutes (9 Hours)] [3]

The study demonstrated the progressive increase in effect as the dose increased from 1 to 3 hours and from 3 to 5½ hours after dosing the mean pH was consistently raised after the 10mg dose, with a pH rise to approximately 4.0. The onset of effect on gastric pH for both the 5mg and 10mg doses was approximately 1.5 hours and the duration of effect, 9 hours. The data suggest that the 10mg dose could be investigated further.

[redacted]

Bioavailability

An in-vivo study to assess bioequivalence across the range of tablet strengths, i.e. between famotidine tablets 10mg, the subject of this application, and the previously licensed Pepcid Tablets, 20 and 40mg, has not been presented. The pharmaceutical assessor states that in the light of the formulation differences between famotidine 10mg, and Pepcid 20mg tablets being similar to those between Pepcid 20mg and 40mg tablets, data to compare the in-vitro dissolution profile of famotidine 10mg film coated tablets with that of Pepcid tablets 20 and 40mg should be provided.

The applicant has looked at the absolute bioavailability of the famotidine 10mg film coated tablet using the intravenous solution of famotidine 10mg as the reference formulation. Absolute bioavailability of 49% was demonstrated.

This is consistent with previously reported figures of 43% for the 20mg film coated tablet and 40% for the 40mg film coated tablet.

A further study assessed the bioavailability/bioequivalence of the film coated tablet and the chewable tablet of famotidine 10mg. The two formulations were found to be well tolerated and based on 90% confidence intervals for the ratios for AUC and C_{max} the film coated and the chewable tablet formulations can be considered bioequivalent.

4.4 **Clinical Efficacy** - see Appendix II for Study summaries.

The clinical efficacy section of the dossier comprises 7 studies, two of which were designed to evaluate famotidine in spontaneously occurring intermittent heartburn, and five designed to determine whether famotidine could reduce symptoms expected following a provocative meal.

Comment on clinical efficacy

Studying a population of future users of a drug which will be available ultimately through pharmacies as an "over the counter" medicine, but is currently only available on prescription, is not easy. In an attempt to do this the applicant has selected patients for entry into studies who self medicated with antacids at least three time per week, where symptomology included the symptom of heartburn and who in 5 of the 7 studies in the clinical programme had the ability to identify specific provocative foods and/or beverages. Further to the difficulties encountered in identifying and recruiting the appropriate population of patients it must be remembered that the primary study end points in the multiple dose studies over time will be recorded by the patient at home and will rely on the patient's self assessment of response. The applicant did perform one study (Protocol 017) in which patients underwent endoscopy and motility studies pre and post trial medication. This study did provide insight into the degree of oesophageal abnormality and peptic ulceration in the population of patients entering the study and also permitted an assessment of treatment on these finding.

One of questions to be addressed in this application is whether self treatment of intermittent heartburn with low dose famotidine is effective and of benefit to the patient. To demonstrate efficacy of famotidine administration should provide a significant improvement over placebo or equivalent benefit to that seen with antacids and ideally improve upon that benefit, or provide benefit to a sub-section of the population in whom antacids have little or no effect. This latter issue has not been addressed in this application.

The patients recruited into the intermittent heartburn trials were all patients who self medicated with antacid on at least 3 occasions per week for the management of heartburn. The results of these studies show that both famotidine and antacid were more effective than placebo in the relief of heartburn; in Protocol 017 it would appear that famotidine 10mg and 20mg were more effective than famotidine 5mg and antacid and in Protocol 019 famotidine 10mg was as effective as antacid but famotidine 20mg appeared superior on global evaluation.

In the provocative meal trials Protocol 020 does provide evidence that famotidine at all 3 doses studied and administered one hour prior to a test meal reduces symptoms of meal related heartburn. The results are less convincing in the other 4 studies in that part of the clinical programme but the changes seen are all in the same direction. The administration of famotidine 1 hour prior to a provocative meal did appear more effective than administration of the drug immediately prior to food.

In summary, the clinical programme does demonstrate efficacy of famotidine over placebo in the management of intermittent heartburn and in heartburn relief following a provocative meal. In the management of intermittent heartburn famotidine is at least as effective as antacid and in Protocol 017 both the 10 and 20mg doses provided greater relief than the 5mg dose and antacid.

The applicant has chosen a single dose of 10mg with a maximum dose in 24 hours of 20mg and although there is some evidence in the second study of intermittent heartburn, Protocol 019, that the 20mg dose does have advantages over the 10mg dose, the remainder of the clinical programme would support the 10mg dose. The selection of the 10mg dose is supported not only by clinical data but also in its effect on gastric pH.

[redacted]

With reference to the effect of famotidine in comparison with antacid it should be noted that the acid neutralising capacity of the antacids used in the clinical programme was low (11 mEq), an ANC which only just falls within the range of 10 to 53 mEq ANC provided by antacids regularly used in the USA.

It would appear that the clinical programme has been carried out using Blocazide 10mg film coated tablets. In the light of the findings of the study to assess bioequivalence across the two 10mg formulations - the film coated and the chewable tablets - no further studies, using the chewable tablets, are required. See Section 4.3.4.

The clinical trial programme described in the application has assessed a population of patients with the target symptom of heartburn. The applicant has listed 7 terms, including heartburn in the list of indications for which Blocazide might be used in management. Six of these 7 symptoms have not been assessed per se, although the difficulties in defining symptoms, assessing change in symptoms and in the multiple variations in symptom nomenclature across the population studied is well recognised. The Committee may wish to consider whether the terms listed under indications are all acceptable following the demonstration of relief of "heartburn" only in the studies presented and whether it would be appropriate to restrict the indication to the "short-term symptomatic relief of heartburn, dyspepsia and hyperacidity" in line with those currently permitted for antacids.

4.5 Safety

The first marketing authorisation for famotidine in tablet formulation was received in Japan in January 1985. Since then famotidine has been registered in 65 countries. It is estimated that over 18 million patients have been treated world wide including over 70,000 patients in post marketing studies for prescription indications. The applicant has assessed safety by looking at the different populations of users of famotidine:

i) Safety data generated from 15 studies performed specifically for the over the counter (OTC) indications which include the clinical programmes completed and submitted in this application.

ii) A review of the safety profile of famotidine following prescription use.

iii) The safety profile of famotidine by body system which includes data generated from all clinical studies, both pre and post marketing, marketed use and literature reports.

iv) A review of the potential for famotidine to interact with other drugs.

[redacted]

Comment on Safety

A comprehensive safety review has been presented by the applicant.

Famotidine would appear to be a safe drug when used in prescribed doses, when used in the clinical efficacy programme presented with this application and even in overdose. There is no reason to suspect that the adverse event profile seen with the drug to date should change if the drug becomes available at a lower strength, administered intermittently, as proposed in this current application.

The general pattern of adverse events across the clinical trials for both OTC and prescribed use and in the post marketing surveillance studies was similar with adverse events seen in the gastrointestinal and central nervous system more frequently. The incidence of headache should be noted and attention drawn to this in the licence documentation.

Famotidine appears to be free from drug interactions, particularly so in respect of drugs metabolised in the liver by cytochrome P450 but appropriate licence statements and patient information should warn against self medication with famotidine by patients who are currently on other medications either prescribed by their physician or self-prescribed and bought over-the-counter.

Appropriate patient information should also be provided regarding use of the drug in patients with major system disease and particularly in patients with moderate to severe renal failure.

One major concern in respect of safety relative to derogation is the possibility that symptoms of gastric carcinoma and peptic ulcer disease may be masked and hence the diagnosis may be delayed, complications may ensue and ultimate outcome may be to the detriment of the patient. This area has been addressed only briefly by the applicant and with reference to the considerations of the American College of Physicians when it evaluated the need for diagnostic evaluation in dyspepsia.

The scenario described is unlikely to occur as the management proposed in this application, with a limit of a maximum of two weeks' treatment before seeking medical advice, only mimics that advice currently advocated at the primary care level. Self medication with famotidine is no more likely to mask the symptoms of gastric carcinoma or peptic ulcer disease than the current management with prescribed H_2 antagonists or antacids. Epigastric pain is a manifestation of dyspepsia but it is also a cardinal symptoms of many more serious underlying pathologies. Therefore the recommendation that OTC use of famotidine be limited to 2 weeks is very appropriate and patients should be instructed that they should seek medical advice if symptoms have not resolved at the end of two weeks' treatment or if symptoms continue to worsen despite treatment. Of some concern would be those patients who do obtain some relief and continue treatment with self-prescribed famotidine "indefinitely" - cost may not be prohibitive to all.

Alongside this recommendation the middle aged and elderly patients should be advised to seek medical advice if they experience new symptoms, a change in the nature of symptoms where an ulcer has been diagnosed previously or where there is unexpected weight loss. Such patients should seek medical advice prior to using OTC famotidine.

Another area which raises concern is the patient on NSAIDs in whom induced gastric mucosal damage may be masked and hence diagnosis may be delayed with prolongation of the risk of acute or chronic bleeding. Therefore, appropriate patient information must be available such that self medication with famotidine should not be undertaken by patients requiring other regular medication unless under the direction of a physician.

Finally, mention should be made of the proposed age range for self-medication with famotidine. The applicant requests Pharmacy status for the use of famotidine at a dose of 10mg, and up to 20mg daily, in adults and children 12 years of age or older. The clinical trial programme presented with this application studies a population of patients aged 18 years and above and in the lack of a recommendation for use of famotidine in children when prescribed, the Committee may wish to consider whether the recommendation for use of these over-the-counter formulations should be for children aged 16 years or older, rather than 12 years.

In conclusion, there is no reason why a licence should not be granted on grounds of safety, providing appropriate warnings are conveyed to the patient.

[redacted]

4.8 Patient Information Leaflet

A patient information leaflet which will be contained within each pack of Blocazide has been submitted by the applicant.

The patient information leaflet is brief and with the exception of patients who are pregnant or breast feeding there is no information provided regarding patient groups in whom Blocazide should not be used without prior consultation with the patient's primary care physician. Blocazide should not be used by certain patients and these should be clearly stated in terms that can be easily understood and which allow no margin for doubt by the user. The areas to be addressed in this respect are as listed in the final recommendations on this application.

The patient information leaflet submitted by the applicant is presented in Appendix V.

4.9 Labelling

Labelling for the cartons for the blister packs (film coated tablets), the cartons for the strip packs (chewable tablets) and for the bottles has been submitted by the applicant.

Labels for the blister packs for the film coated tablets and the aluminium foil strip packs for the chewable tablets has not been submitted. These will be requested.

The following amendments to the labelling submitted should be considered:-

4.9.1 The labels should be clearly marked such that the prospective patient will understand that Blocazide should not be used if he/she suffers from any other illness, is taking any other regular medicines or is being seen regularly by his/her GP or by any hospital doctor.

4.9.2 The descriptors "rapid", "acid controller" and "new" are inappropriate and should be deleted.

4.9.3 The clarity of the dosage recommendations could be improved.

4.9.4 Any changes to the licence documentation subsequent on the review of this application will need to be reflected in the wording on the labelling.

The labelling submitted by the applicant is presented in Appendix VI.

4.10 **MLA 201 Form and Summary of Product Characteristics (SPC)**

The MLA 201 form and SPC will require revision before any licence based on them can be issued to incorporate changes as directed by the final recommendations on this application.

4.11 **Legal Status - Derogation**

The applicant is seeking product licences for Blocazide Film Coated Tablets and Blocazide Chewable Tablets, each formulation containing famotidine 10mg and has requested Pharmacy Status.

Famotidine in prescribed doses has been shown to be safe.

The proposed application is made in request of a lower total daily dose taken for a maximum period of 2 weeks, following which time, if symptoms persist, medical consultation is recommended. Providing appropriate information in respect of the use of famotidine 10mg, particularly regarding dose, duration of treatment and contraindications to use, is made clearly available to both pharmacists and patients, this product, Blocazide, could be granted pharmacy status. Ability of the patient to read and understand the patient instructions must be borne in mind when this product is dispensed by the pharmacist.

Pharmacy status has been requested for the treatment of indigestion, acid indigestion, nervous indigestion, heartburn, dyspepsia, acidity and symptoms of upset stomach associated with these conditions. The applicant has submitted a clinical dossier demonstrating efficacy of famotidine 10mg in the management of self diagnosed heartburn, both intermittent and following provocative foods/beverages, when compared with placebo. It is recommended that pharmacy status could be granted on the basis of these clinical findings for the short-term symptomatic relief of heartburn, hyperacidity and dyspepsia. Efficacy data for other symptoms listed have not been provided.

4.12 **Recommendation**

It is recommended that product licences should be granted for Blocazide 10mg Tablets, (Film Coated and Chewable Tablets), both formulations containing famotidine 10mg, for use for the short-term symptomatic relief of heartburn, hyperacidity and dyspepsia. Use should be restricted to patients aged 16 years and above.

[redacted]

[redacted]

[redacted]

DATE: May 1993 **CSM/CPS/SCOP/SESC/93/5th Meeting**

NUMBER: PL 0025/0312 **COMPANY:** Merck Sharp & Dohme Ltd **PRODUCT:** Blocazide 10mg Film-coated Tablets **THERAPEUTIC CLASS:** H_2-receptor antagonist **ACTIVE CONSTITUENT:** Famotidine 10mg	**SUB-COMMITTEE ON PHARMACOVIGILANCE** **APPLICATION FOR NON-PRESCRIPTION AVAILABILITY** **DRAFT RECOMMENDATION** **Draft advice on legal classification** The Sub-Committee considered whether Blocazide (the product) falls within a description or class specified for the purpose of section 58 of the Medicines Act 1968 by section 58A(2) of that Act, as being appropriate for supply on a prescription only basis and advised that the POM Order be amended to allow non prescription supply. The Committee saw no reason to restrict the exemption from POM control to this particular product and recommended that the change in the POM Order be made to the entry for famotidine 10mg (the drug substance) when used for the short-term symptomatic relief of heartburn, dyspepsia and hyperacidity, in a dose of 10mg as needed to relieve symptoms, or one hour before eating for symptoms associated with food and beverage, to a maximum daily dose of not greater than 20mg for the treatment period of not greater than 2 weeks.

[redacted]

NUMBER:

PL 0025/0312

COMPANY:

Merck Sharp & Dohme Ltd

PRODUCT:

Blocazide 10mg Film-coated Tablets

THERAPEUTIC CLASS:

H_2-receptor antagonist

ACTIVE CONSTITUENT:

Famotidine 10mg

SAFETY AND EFFICACY SUB-COMMITTEE

DRAFT RECOMMENDATION

On the evidence before them, the Sub-Committee recommended the grant of a Product Licence for this preparation provided that the applicant complies with the following conditions:

1. The indication is restricted to "the short-term symptomatic relief of heartburn, dyspepsia and hyperacidity" only.

2. The MLA 201 and SPC should be amended to the satisfaction of the Secretariat in respect of:-

2.1 Recommended doses and dosage schedules.

Clear statements should be made regarding the treatment period as follows:-

2.1.1 The maximum treatment period is 2 weeks.

2.1.2 If symptoms persist after 2 weeks' treatment the patient must seek medical advice.

The recommendations for use in children should be revised as follows:-

2.1.3 Blocazide 10mg is recommended for use in adults and children 16 years of age or older. Blocazide 10mg is not recommended for use in children.

[redacted]

DATE: May 1993 **CSM/CPS/SCOP/SESC/93/5th Meeting**

NUMBER:

PL 0025/0312

COMPANY:

Merck Sharp & Dohme Ltd

PRODUCT:

Blocazide 10mg Film-coated Tablets

THERAPEUTIC CLASS:

H_2-receptor antagonist

ACTIVE CONSTITUENT:

Famotidine 10mg

SAFETY AND EFFICACY SUB-COMMITTEE

DRAFT RECOMMENDATION

2.2 **Contraindications**

Blocazide should be contraindicated in:-

- pregnancy and lactation
- children under 16 years of age
- patients with moderate or severe renal failure
- patients with severe hepatic impairment
- patients under regular medical supervision for other reasons
- patients suffering from any other illness or taking other medications either physician-prescribed or self-prescribed
- patients of middle age or older with new or recently changed dyspeptic symptoms
- patients with unintended weight loss in associated with dyspeptic symptoms.

2.3 **Interactions with other medicaments**

A statement should be included regarding the potential for interaction between famotidine and antihistamines.

2.4 **Other undesirable effects**]
Use in pregnancy and lactation]

These sections should also include the statements made in the licence documentation for the previously marketed strengths of famotidine, as Pepcid.

[redacted]

DATE: May 1993 **CSM/CPS/SCOP/SESC/93/5th Meeting**

NUMBER:

PL 0025/0312

COMPANY:

Merck Sharp & Dohme Ltd

PRODUCT:

Blocazide 10mg Film-coated Tablets

THERAPEUTIC CLASS:

H_2-receptor antagonist

ACTIVE CONSTITUENT:

Famotidine 10mg

SAFETY AND EFFICACY SUB-COMMITTEE

DRAFT RECOMMENDATION

2.5 **Special warnings and precautions**

A statement regarding the possible relationship between famotidine and haematological disorders should be made.

2.6 **Overdose**

A statement should be included regarding management in those patients who do overdose with this drug.

2.7 **Incompatibilities**

This statement should read as "none known".

3. The patient information leaflet should be amended to the satisfaction of the Secretariat in respect of:-

3.1 Those groups of patients in whom Blocazide should not be used without prior medical consultation who should be clearly stated, as listed above under 2.2.

3.2 The list of other constituents which should be completed in line with the MLA 201 form, page 7.

3.3 The occurrence of headache and dizziness and possibly gastrointestinal tract symptoms, which should be described.

[redacted]

DATE: May 1993 **CSM/CPS/SCOP/SESC/93/5th Meeting**

NUMBER:

PL 0025/0312

COMPANY:

Merck Sharp & Dohme Ltd

PRODUCT:

Blocazide 10mg Film-coated Tablets

THERAPEUTIC CLASS:

H_2-receptor antagonist

ACTIVE CONSTITUENT:

Famotidine 10mg

SAFETY AND EFFICACY SUB-COMMITTEE

DRAFT RECOMMENDATION

3.4 The paragraph which describes "How do the tablets work?" which should be revised and the descriptors, "rapid", "small" and "easy to swallow" should be deleted.

4. The product labelling should be amended to the satisfaction of the Secretariat particularly in respect of:-

4.1 Clear marking such that the prospective patient will understand that Blocazide should not be used if he/she suffers from any other illness, is taking any other regular medicines or is being seen regularly by his/her GP or by any hospital doctor.

4.2 The use of descriptors "rapid", "acid controller" and "new" should be deleted.

4.3 The clarity of the dosage recommendations.

Labels for the blister packs for the film coated tablets should be submitted.

[redacted]

NUMBER:

PL 0025/0312

COMPANY:

Merck Sharp & Dohme Ltd

PRODUCT:

Blocazide 10mg Film-coated Tablets

THERAPEUTIC CLASS:

H_2-receptor antagonist

ACTIVE CONSTITUENT:

Famotidine 10mg

SAFETY AND EFFICACY SUB-COMMITTEE

DRAFT RECOMMENDATION

5. **Draft advice on legal classification**

The Sub-Committee considered whether Blocazide (the product) falls within a description or class specified for the purpose of section 58 of the Medicines Act 1968 by section 58A(2) of that Act, as being appropriate for supply on a prescription only basis and advised that the POM Order be amended to allow non prescription supply.

The Committee saw no reason to restrict the exemption from POM control to this particular product and recommended that the change in the POM Order be made to the entry for famotidine 10mg (the drug substance) when used for the short-term symptomatic relief of heartburn, dyspepsia and hyperacidity, in a dose of 10mg as needed to relieve symptoms, or one hour before eating for symptoms associated with food and beverage, to a maximum daily dose of not greater than 20mg for the treatment period of not greater than 2 weeks.

[redacted]

2 LABELLING

2.1 Film-coated Tablets

The following text will appear on the cartons for the blister packs, and the label for the bottles:

FRONT PANEL:

New
BLOCAZIDE™
ACID CONTROLLER
Rapid Relief from indigestion and heartburn.
BLOCAZIDE™ has been clinically proven to control excess stomach acid for up to 9 hours.
'X' tablets

BACK PANEL:

BLOCAZIDE™ Tablets
Famotidine 10 mg

For the treatment of indigestion, acid indigestion and nervous indigestion, heartburn, dyspepsia, excess acid and upset stomach.

DOSAGE: Adults and children over 12 years: Take one tablet as required, or for symptoms usually associated with food and/or beverage take one tablet one hour before eating. Repeat if symptoms return, up to a maximum of 2 tablets in a 24-hour period.

If symptoms persist for more than 2 weeks, consult your doctor.

Do not take if you are pregnant or breast-feeding except on a doctor's advice.

If you have difficulty swallowing, or persistent abdominal discomfort, consult your doctor.

Inactive ingredients: Red Iron Oxide and Titanium Dioxide.

Keep all medicines safely away from children.

'X' tablets

P

Product Licence No: 0025/0312
Product Licence Holder: Merck Sharp and Dohme Ltd Dist by: JJ/MSD*
Hertford Road
Hoddesdon
Herts En11 9BU

™ Trademark

Company logo

Bar code

BASE PANEL:

BLOCAZIDE™
ACID CONTROLLER

Expiry date:
Batch No:

SIDE PANELS:

BLOCAZIDE™
'X' tablets

TOP PANEL:

BLOCAZIDE™
ACID CONTROLLER
'X' tablets

Note:

The distributor may or may not be included

'X' refers to the number of tablets

[redacted]

Product	Blocazide	Code	
Item	Patient Information Leaflet		
Based on			
Typist	[redacted]		
Writer			
Technical Approval	[redacted]	Date	
Legal Approval		Date	

Blocazide™

(famotidine)

WHAT IS IN THE TABLETS?

Each tablet contains 10 mg of famotidine as the active ingredient. They also contain: Hydroxypropylcellulose EP, Methylhydroxypropylcellulose EP, Red iron oxide EP, Magnesium stearate EP, Microcrystalline cellulose EP, Pregelatinised maize starch BP, Talc EP, Titanium dioxide BP.

This pack contains ?? tablets.

HOW DO THE TABLETS WORK?

'Blocazide' is a new therapy that provides rapid relief from indigestion and heartburn with just one small tablet. It has been clinically proven to control excess stomach acid for up to nine hours. Unlike antacids which neutralise acid, 'Blocazide' contains famotidine, an ingredient that actually controls the flow of excess acid and treats the cause of pain and discomfort. 'Blocazide' is available in easy-to-swallow tablets.

Continuation Sheet Number 2

Product	Blocazide	Code
Item	Patient Information Leaflet	

Product licence holder:

Merck Sharp & Dohme Limited

Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU

Manufacturer:

Name

Address

WHAT ARE 'BLOCAZIDE' TABLETS USED FOR?

'Blocazide' Tablets are for the treatment of indigestion, acid indigestion, nervous indigestion, heartburn, dyspepsia, acidity, and symptoms of upset stomach.

CHECK BEFORE YOU TAKE THIS PRODUCT

Ask your doctor before taking the tablets if you are pregnant or breast-feeding.

HOW SHOULD YOU TAKE 'BLOCAZIDE'?

Adults, and children 12 years of age or older:

- Take 1 tablet as needed to relieve indigestion, acid indigestion, nervous indigestion, heartburn, dyspepsia, acidity, and symptoms of upset stomach, or 1 tablet one hour before eating to relieve symptoms usually associated with food and drink.
- Repeat the dose if symptoms persist, up to a maximum of 2 tablets in a 24-hour period.
- Do not take for more than two weeks except on the advice of your doctor.

[redacted]

Continuation Sheet Number 3

Product	Blocazide	Code
Item	Patient Information Leaflet	

Also, consult your doctor promptly if you have difficulty swallowing, or persistent stomach pains.

WILL THE TABLETS SUIT YOU?

Most people do not suffer side effects when taking 'Blocazide'. If you think you are reacting badly in any way, stop your treatment and see your doctor.

STORING YOUR TABLETS

'Use by' date: Do not use 'Blocazide' Tablets if they are past the expiry date on the box.

Remember: Keep all medicines out of the reach of children.

Date of first printing ...

FAMOTIDINE OTC FILM-COATED TABLETS	TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER PART IIA: COMPOSITION

Product Description

A pale-rose (pink) colored, rounded-square, film-coated tablet with the Trademark printed on one side.

Complete Composition Page A3

Active Ingredient

	mg/tablet
Famotidine USP	10.0

Other Ingredients

Tablet Core:
Starch Pregelatinized BP, NF
Microcrystalline Cellulose EP, NF
Alcohol SD3A Anhydrous
(or Alcohol USP 95%)
Purified Water EP, USP
Talc EP, USP
Magnesium Stearate EP, NF

Tablet Coat:
Hydroxypropyl Methylcellulose
EP, USP 6 cps
Hydroxypropyl Cellulose LF, EP, NF
with < 0.3% Silica
Titanium Dioxide/E171, USP
Talc EP, USP
Red Ferric Oxide/E172 NF
Purified Water EP, USP

[redacted]

Qualitatively the same as Pepcid 20 mg and 40 mg tablets, although the three strengths are not in scale to each other.

[redacted]

FAMOTIDINE
OTC
FILM-COATED
TABLETS

TABULAR SUMMARIES
REFERRING TO PART II
OF THE DOSSIER

PART IIA: COMPOSITION

[redacted]

The targeted film-coated tablet weight is [redacted]

Containers and Closures Pages A7, A8, and A9

The primary packages for famotidine are a) HDPE bottles, b) aluminum foil strip packages and c) PVC/foil blister packages.

The bottle closure consists of LDPE, non-CR, snap cap with liner or PP, CR, cap with liner. The aluminum strip package consists of paper/LDPE, non-CR foil or non-CR paper/poly strip. The blister package consists of PVC with non-CR foil or CR peelable foil. Alternative packages are PET/LDPE/Foil CR and non-CR strips and PVC/PE/PVDC or PVC/PE/Aclar with Cr or non-CR foil.

Use of non-child resistant closure undesirable. No justification given.

The 'alternative packages' are not proposed for marketing.

Clinical Trial Formulations Pages A10-A21

The formulations of famotidine used to support clinical trials are provided. A preliminary chewable tablet formulation was used in a probe bioequivalence study. Sterile intravenous solutions were provided as clinical controls. Antacid products were incorporated in various studies as controls, when required. Placebo formulations were included in studies, when required.

[redacted]

Formulation of Famotidine Film-Coated Tablet (AF) Proposed for Marketing

	mg/tablet
Tablet Core:	
Famotidine USP	10.0
Starch Pregelatinized BP, NF	[redacted]
Microcrystalline Cellulose EP, NF	
Alcohol SD3A Anhydrous (or Alcohol USP 95%)*	
Purified Water EP, USP*	
Talc EP, USP	
Magnesium Stearate EP, NF	
Tablet Coat:**	
Hydroxypropyl Methylcellulose, EP, USP 6 cps	
Hydroxypropyl Cellulose LF, EP, NF with <0.3% Silica	
Titanium Dioxide/E171 EP, USP	
Talc EP, USP	
Red Ferric Oxide/E172 NF	
Purified Water EP, USP*	

[redacted]

Film-Coated Tablet Formulations Used in Clinical Studies

Formula Designation	BF	CF	DF	EF	FF	GF	PFI
Tablet Core							
Famotidine USP	0.50	2.50	5.00	10.0	20.0	5.00	–
Microcrystalline Cellulose NF	[redacted]						
Pregelatinized Starch NF							
Magnesium Stearate NF							
Talc USP							
Alcohol SD3A Anhydrous*							
Purified Water USP*							
Film-Coating							
Hydroxylpropyl Methylcellulose USP 6 cps	[redacted]						
Hydroxypropyl Cellulose LF NF with < 0.3% Silica							
Titanium Dioxide USP							
Talc USP							
FD&C Blue No. 1							
Red Ferric Oxide NF							
Purified Water USP*							
[redacted]							

FAMOTIDINE OTC FILM-COATED TABLETS

TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER

PART IIA: COMPOSITION

Intravenous Solution (IV) Used in Clinical Studies *

	mg/mL
Famotidine USP	10.0
L-Aspartic Acid	[redacted]
Mannitol USP	
Water for Injection qs to	

[redacted]

Proposed Market Formulation of Famotidine Chewable Tablets (AC) Used in Clinical Studies

Uncoated Famotidine Rotogranulation:	mg/tablet
Famotidine USP	10.0
Lactose EP NF	[redacted]
Hydroxypropyl Methylcellulose EP, USP	
Purified Water EP, USP*	
Particle Coating:	
Cellulose Acetate NF	
Hydroxypropyl Cellulose EF, EP, NF	
Acetone NF*	
Methanol NF*	
Final Blending/Compression:**	
Mannitol EP, USP	
Microcrystalline Cellulose EP, NF	
Aspartame NF	
Prosweet Powder #694	
Magnesium Stearate EP, NF	
Trusil Natural Peppermint 3X	
Red Ferric Oxide/E172 NF	

[redacted]

[redacted]

FAMOTIDINE OTC FILM-COATED TABLETS

TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER

PART IIA: COMPOSITION

Preliminary Chewable Tablet Formulations Used in Clinical Studies

	mg/tablet	
Formulation Designation	BC	CC
Uncoated Famotidine Rotogranulation:		
Famotidine USP	5.00	10.0
Lactose NF	[redacted]	
Povidone USP		
Hydroxypropyl Methylcellulose USP		
Purified Water USP*		
Particle Coating:		
Cellulose Acetate NF		
Povidone USP		
Hydroxypropyl Cellulose EP, NF		
Acetone NF*		
Methanol NF*		
Final Blending/Compression:**		
Mannitol USP		
Microcrystalline Cellulose NF		
Aspartame NF		
Prosweet Powder #6894		
Magnesium Stearate NF		
Trusil Natural Peppermint 2X		
Red Ferric Oxide NF		
[redacted]		

Note inclusion of povidone.

[redacted]

FAMOTIDINE
OTC
FILM-COATED
TABLETS

TABULAR SUMMARIES
REFERRING TO PART II
OF THE DOSSIER

PART IIA: COMPOSITION

Antacid Tablet Formulation Used in Clinical Studies
Recompressed GELUSIL Tablets (HF)

	mg/tablet
GELUSIL Tablets	1200
Magnesium Stearate NF	[redacted]

Placebo Antacid Tablet Formulations (PF2) Used in Clinical Studies

	mg/tablet
Dibasic Calcium Phosphate USP	400
Confectioners Sugar NF with 3% Starch	[redacted]
Mannitol USP	
Corn Starch NF	
Purified Water USP*	
Imitation Vanilla Firmenich 50471 T	
Colloidal Silicon Dioxide NF	
Corn Starch NF	
Magnesium Stearate NF	
Alcohol SD3A Anhydrous*	
Trusil Natural Peppermint 3X	
[redacted]	

Development Pharmaceutics Pages A22-A37

The product development objective was to develop a tablet of famotidine for a product line intended for the OTC market. This was accomplished by using the experience gained during the development of the currently marketed prescription strength of famotidine tablets, 20 mg and 40 mg. Early prescription dosage form development also included 5 mg and 10 mg potencies.

The development of the final market image film-coated tablet, for OTC use, was based primarily on the results of the currently marketed prescription strength and the development and probe stability studies of the proposed OTC product.

In-vitro dissolution profiles of Blocazide tablets 10 mg, Pepcid tablets 20 mg and 40 mg should be compared.

[redacted]

FAMOTIDINE OTC FILM-COATED TABLETS	TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER PART IIA: COMPOSITION

Development Pharmaceutics (Cont.)

[redacted]

Used to select proposed marketing pack.

The color difference from that proposed for marketing is unlikely to effect bioavailability.

[redacted]

Full details provided.

Should also be controlled in finished product.

Manufacturing of clinical supplies and batches for use in container stability studies indicate that product which conforms to specifications has been consistently manufactured.

Famotidine can exist in two polymorphic forms (I and II) - see insert.

Capsule-shaped tablets used in some clinical studies have a similar in-vitro dissolution profile to the rounded-square shaped tablets proposed for marketing (see insert).

[redacted]

4.1.2 Film-Coated Tablet Development (Cont.)

These polymorphic forms were extensively studied prior to the filing of the Marketing Authorization Application for famotidine tablets. This information is directly applicable for the famotidine tablets intended for OTC use.

Famotidine tablets prepared by Merck & Co., Inc. uses the Form I crystalline type. The same Form I famotidine was also used in all Merck-sponsored clinical studies and in the OTC market image tablets. The differences between properties of the two forms such as aqueous solubility and DSC endotherm are relatively small, as shown in Table A5.

Table A5 Aqueous Solubility and DSC Endotherms of Form I and Form II Famotidine

	Form I	Form II
Aqueous Solubility (20°C)	0.73 mg/mL	0.59 mg/mL
DSC Endotherm	164°C	173°C

In addition, dissolution profiles of tablets made from the two polymorphic forms were similar (Table A6).

Table A6 Comparative Dissolution Rates of Famotidine Crystalline Forms I vs II

	% Label Claim Dissolved	
	Form I (0208 FCT 012 E 002)	Form II (0208 FCT 022 E 001)
15 min	98, 101, 97, 99, 98, 97 Mean = 98	96, 96, 96, 99, 98, 97 Mean = 97
30 min	100, 100, 100, 100, 100, 100 Mean = 100	100, 100, 100, 100, 100, 100 Mean = 100

Comparative dissolution data for capsule-shaped and rounded-square film-coated tablets used clinically and the proposed market image for OTC use were also similar as shown in Table A7.

To examine if oral absorption of famotidine was different between the two polymorphic forms, Yamanouchi earlier conducted two studies in dogs and in humans and found that the two forms were bioequivalent when administered in capsule dosage form [Part IVQ, Reference 5]

These data, together with the bioequivalency data in Part IVQ, support the position that Form I and Form II are not

MSD

Table A7 Comparative Dissolution Rates of Capsule-Shaped and Rounded-Square Famotidine Tablets

Batch: 0208 FCT 011 D 003
Shape: Capsule-shaped
Color: Blue

Minutes	% of Label Claim Dissolved 10	20	30
	97	97	98
	96	97	97
	96	97	97
	95	96	96
	96	96	96
	96	97	97
	98	98	98
	98	98	98
	95	97	97
	97	97	98
	96	97	98
	97	98	98
Mean =	96	97	97

Batch: 0208 FCT 038 D 001
Shape: Rounded-square
Color: Pale-rose (pink)

Minutes	% of Label Claim Dissolved 10	20	30
	96	97	97
	98	98	99
	96	97	96
	96	96	96
	97	97	98
	95	96	96
	96	96	97
	96	97	96
	97	97	98
	98	99	99
	99	99	99
	98	99	99
	97	98	98
	98	99	100
	97	98	98
	98	99	99
	97	97	98
	98	97	98
Mean =	97	98	98

MSD

Table E12 Summary of Studies Conducted by Yamanouchi Pharmaceutical Co. Showing no Bioavailability Differences Between the Two Polymorphic Forms (Mean ± s.e.) [5]

		Form I	Form II
Dogs (N=6)	0-10 hr [AUC], ng•hr/mL	1724 ± 144	1696 ± 118
	T_{max}, hr	1.5 ± 0.3	1.7 ± 0.2
	C_{max}, ng/mL	468 ± 55	520 ± 38
	Half-life, hr	2.3 ± 0.1	2.2 ± 0.1
Humans (N=12)	0-12 hr [AUC], ng•hr/mL	339 ± 30	336 ± 31
	T_{max}, hr	2.7 ± 0.2	2.8 ± 0.3
	C_{max}, ng/mL	67.2 ± 4.5	72.3 ± 5.3
	Half-Life, hr	2.9 ± 0.2	2.8 ± 0.3

4.1.2 Film-Coated Tablet Development (Cont.)

substantially different and are equally available as measured by in vivo and in vitro methods. [redacted]

[redacted]

[redacted]

FAMOTIDINE OTC FILM-COATED TABLETS	TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER PART IIA: COMPOSITION

Explanation of Choice of the Composition

The functions of the product ingredients are as follows:

Component	Function
Famotidine	Histamine H_2-receptor antagonist/Active Agent
Pregelatinized Starch	Filler/binder/ disintegrant
Microcrystalline Cellulose	Binder/filler
Talc (tablet core)	Glidant/lubricant adjunct
Magnesium Stearate	Lubricant
Hydroxypropyl Methylcellulose	Polymeric film former
Hydroxypropyl Cellulose	Polymeric film former
Titanium Dioxide	Opacifier
Talc (coating)	Opacifier adjunct
Red ferric oxide	Colorant

[redacted]

FAMOTIDINE OTC FILM-COATED TABLETS	TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER PART IIB: METHOD OF PREPARATION

Manufacturing Formula Page B2

Batch Size: [redacted] tablets

	kg [redacted] tablets
Core:	
Famotidine USP	4.0
Starch Pregelatinized NF (weight allowance)*	[redacted]
Microcrystalline Cellulose EP, NF (weight allowance)*	
Alcohol SD3A Anhydrous (or Alcohol USP 95%)	
Purified Water, EP, USP	
Talc EP, USP	
Magnesium Stearate EP, NF	
Tablet Coat:	
Hydroxypropyl Methylcellulose EP, USP 6 cps	[redacted]
Hydroxypropyl Cellulose LF, EP, NF with <0.3% Silica	
Titanium Dioxide/E171 USP	
Talc EP, USP	
Red Ferric Oxide/E172 NF	
Purified Water EP, USP	

[redacted]

[redacted]

[redacted]

FAMOTIDINE OTC FILM-COATED TABLETS	TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER PART IIB: METHOD OF PREPARATION

Manufacturing Process Page B4 and B5

Famotidine, microcrystalline cellulose, and pregelatinized starch are granulated with a hydroalcoholic solution, dried, milled, lubricated with magnesium stearate and talc, and compressed into tablets.

Conventional process.

The tablet coating suspension is prepared by dispersing the hydroxypropyl methylcellulose and hydroxypropyl cellulose in the purified water and then dispersing the titanium dioxide, talc and red ferric oxide in this suspension. Film-coating suspension is applied to compressed tablets in a coating pan by spraying.

In-Process Controls Page B6

The uncoated tablets are tested to meet the following in-process control guides:

Dried granulate is also controlled: moisture [redacted]

Appearance	White, rounded-square-shaped tablet
Weight of 10 tablets	[redacted]
Hardness (measured diagonally)	
Thickness	
Disintegration	

[redacted]

[redacted]

FAMOTIDINE OTC FILM-COATED TABLETS	TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER PART IIB: METHOD OF PREPARATION

Assembly Process Page B7

Blister units are formed, filled and sealed on automatic machinery, and inserted, with leaflets, into cartons on automatic carton machinery. Batch number, date of manufacture (carton only) and expiry date are marked on each blister and carton by the machine. The cartons are overwrapped with transparent film.

Bottles are filled, capped and labeled on fully automatic lines. The labels are overprinted on the labelling machine with batch number, date of manufacture, and expiry date. The bottles are overwrapped with transparent film.

Tablets are assembled in foil pouches on automatic fill and seal machines. Printing and packaging of the pouches follows a similar process as described for the blister units.

Process Validation Page B11

[redacted]

All manufacture to date at MS & D, West Point, Pennsylvania, USA. Process validation protocols needed for Woelm Pharma, Germany; MS & D, Cramlington, UK; MS & D, Pavia, Italy - where routine production will occur.

[redacted]

FAMOTIDINE OTC FILM-COATED TABLETS	TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER PART IIC: CONTROL OF STARTING MATERIALS

Control of Starting Materials: Active Ingredient

Specification and Routine Tests Page C1 & Reference 3

a) Active Ingredients Described in a Pharmacopoeia
Famotidine USP

Satisfactory, MS & D are the UK originators.

See insert for USP monograph.

b) Active Ingredients Not Described in a Pharmacopoeia
Not Applicable

Structural Relationship to Other Known Drugs
Famotidine is a histamine H_2 -receptor antagonist.

Nomenclature Pages C1 and C2

INN
Famotidine

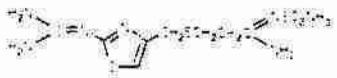
WHO
1-Amino-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propylidene]sulfamide

IUPAC
3-{[2-(Diaminomethylenamino)-4-thiazolyl]methylthio}-N^2-sulfamoylpropanamidine

USAN
N-(Aminosulfonyl)-3[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propanimidamide

[redacted]

Famotidine



$C_8H_{15}N_7O_2S_3$ 337.43
Propanimidamide, *N'*-(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]-methyl]thio]-.
[1-Amino-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]-methyl]thio]propylidene] [*76824-35-6*].

» Famotidine contains not less than 98.5 percent and not more than 101.0 percent of $C_8H_{15}N_7O_2S_3$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers, protected from light.

Reference standard—*USP Famotidine Reference Standard*—Dry at a pressure between 1 mm and 5 mm of mercury at 80° for 5 hours before using.

Identification—

A: The ultraviolet absorption spectrum of a solution (1 in 40,000) in *Phosphate buffer* exhibits maximum and minimum at the same wavelengths as that of a similar solution of USP Famotidine RS concomitantly measured, and the respective absorptivities, calculated on the dried basis at the wavelength of maximum absorbance at about 265 nm do not differ by more than 3.0%. [NOTE—Prepare the *Phosphate buffer* as follows. Adjust 250 mL of 0.02 *M* phosphoric acid with sodium hydroxide solution (1 in 10) to a pH of 2.5, dilute with water to 500 mL, and mix.]

B: The infrared absorption spectrum of a potassium bromide dispersion of it, previously dried, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Famotidine RS.

Loss on drying ⟨731⟩—Dry it at a pressure between 1 mm and 5 mm of mercury at 80° for 5 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩: not more than 0.001%.

Chromatographic purity—

Test preparation—Prepare a solution in glacial acetic acid containing 20 mg of Famotidine per mL.

Standard preparations—Dissolve USP Famotidine RS in glacial acetic acid to obtain a solution having a known concentration of 0.2 mg per mL. Dilute portions of this solution quantitatively with glacial acetic acid to obtain *Standard preparations A, B, C,* and *D*, containing 100 µg, 60 µg, 40 µg, and 20 µg of the *Reference standard* per mL, respectively.

Procedure—On a suitable high performance thin-layer chromatographic plate (see *Chromatography* ⟨621⟩), coated with a 0.25-mm layer of chromatographic silica gel mixture, apply separately 5 µL of the *Test preparation* and 5 µL of each *Standard preparation*, and dry under a stream of nitrogen. Position the plate in a chromatographic chamber, and develop the chromatograms in a solvent system consisting of a mixture of ethyl acetate, methanol, toluene, and ammonium hydroxide (40:25:20:2) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and air-dry the plate. Examine the plate under short-wavelength ultraviolet light, and compare the intensities of any secondary spots observed in the chromatogram of the *Test preparation* with those of the principal spots in the chromatograms of the *Standard preparations*: no secondary spot from the chromatogram of the *Test preparation* is larger in size or more intense than the principal spot obtained from *Standard preparation A* (0.5%) and the sum of the intensities of the secondary spots obtained from the *Test preparation* corresponds to not more than 2.0%.

Assay—Dissolve about 250 mg of Famotidine, accurately weighed, in 80 mL of glacial acetic acid, and titrate with 0.1 *N* perchloric acid VS (see *Titrimetry* ⟨541⟩), using a suitable anhydrous electrode system. Any aqueous electrolyte solution contained in the electrodes employed should be removed, the electrode rendered anhydrous and filled with 0.1 *N* lithium perchlorate in acetic anhydride. Perform a blank determination and make any necessary correction. Each mL of 0.1 *N* perchloric acid is equivalent to 16.87 mg of $C_8H_{15}N_7O_2S_3$.

Famotidine

Change to read:

$C_8H_{15}N_7O_2S_3$ 337.43
Propanimidamide, *N'*-(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]-.
[1-Amino-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]-methyl]thio]propylidene] ■sulfamide■ [*76824-35-6*].

Change to read:

Chromatographic purity—

Test preparation—Prepare a solution in glacial acetic acid containing 20 mg of Famotidine per mL.

Standard preparations—Dissolve USP Famotidine RS in glacial acetic acid to obtain •*Standard preparation A*■ having a known concentration of 0.2 mg per mL.• Dilute a portion of this solution, quantitatively with glacial acetic acid to obtain *Standard preparation B* containing 65 µg of the Reference Standard per mL.■•

•*Procedure*—Apply separately 5 µL of the *Test preparation* and 5 µL of each *Standard preparation* to a suitable high performance thin-layer chromatographic plate (see *Chromatography* ⟨621⟩), coated with a 0.25-mm layer of chromatographic silica gel mixture, and dry under a stream of nitrogen. Position the plate in a chromatographic chamber, and develop the chromatograms in a solvent system consisting of a mixture of ethyl acetate, methanol, toluene, and ammonium hydroxide (40:25:20:2) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and air-dry the plate. Examine the plate under short-wavelength ultraviolet light, and compare the intensities of any secondary spots observed in the chromatogram of the *Test preparation* with those of the principal spots in the chromatograms of the *Standard preparations*: no secondary spot from the chromatogram of the *Test preparation* is larger in size or more intense than the principal spot obtained from *Standard preparation* •*B*(0.3%)■•, and the sum of the intensities of the secondary spots obtained from the *Test preparation* corresponds to not more than •1.0% (*Standard preparation A*)■• •11

Add the following:

■**Organic volatile impurities,** *Method V* ⟨467⟩: meets the requirements.

Solvent—Use dimethyl sulfoxide as the solvent.■

FAMOTIDINE OTC FILM-COATED TABLETS	TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER PART IIC: CONTROL OF STARTING MATERIALS

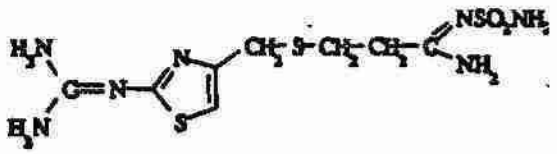
BAN
3-[2-(Diaminomethyleneamino)1,3-thiazol-4-ylmethylthio]-N-sulphamoylpropionamidine

CAS
3-[[[2-[(Aminoiminomethyl)amino]-4-thiazolyl]methyl]thio]-N-aminosulfonyl)-propanimidamide

Description Page C3

Famotidine is a white to yellowish-white free flowing powder.

Structural Formula:



Molecular Formula: $C_8H_{15}N_7O_2S_3$

Relative Molecular Mass: 337.43

Control of Starting Materials-Active Ingredients; Scientific Data (manufacture)

Name and Addresses of Manufacturing Sources Page C3
Famotidine drug substance is manufactured by Yamanouchi Pharmaceutical Company, Ltd., Tokyo 174, Japan and Yamanouchi Ireland Co., Ltd., Dublin 15, Ireland.

Yamanouchi have licensed famotidine to MS & D for certain markets, including the UK.

[redacted]

The MSD specification for famotidine is as follows.

Appearance:	White to pale yellow crystalline powder, free from visible contamination.
Identity:	i) Has the same IR spectrum as the reference standard. ii) Has the same Rf value as the reference standard on TLC examination.
Ultraviolet absorbance A1% 1 cm at 265 ± 2 nm:	[redacted]
Loss on drying:	
Residue on ignition:	
Heavy metals:	
Assay:	
Related substances:	[redacted]

[redacted]

[redacted]

FAMOTIDINE OTC FILM-COATED TABLETS	TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER PART IIC: CONTROL OF STARTING MATERIALS

Synthetic or Manufacturing Route Page C4

Famotidine drug substance is synthesized by the same routes as used for manufacturing prescription strength of famotidine. Complete descriptions of the routes and process controls can be found in the original Famotidine MAA for 20 mg and 40 mg tablets.

Checked as correct.

Control of Starting Materials. Inactive Ingredients--Specifications and Routine Tests

1. Inactive Ingredients Described in a Pharmacopoeia Pages C4 and C5

Satisfactory.

Starch Pregelatinized BP, NF
Microcrystalline Cellulose EP, NF
Magnesium Stearate EP, NF
Talc EP, USP
Hydroxypropyl Methylcellulose EP, USP 6 cps
Hydroxypropyl Cellulose
LF, EP, NF with <0.3% Silica
Titanium Dioxide/E171 USP
Red Ferric Oxide/E172, NF
Purified Water EP, USP
Alcohol USP

The materials are tested to meet composite specifications covering the requirements in all the compendia shown. In addition, Titanium Dioxide and Red Ferric Oxide conform to the requirements (general and specific) given for EEC Permitted Coloring Materials No. E171 and No. E172.

Satisfactory.

[redacted]

FAMOTIDINE OTC FILM-COATED TABLETS	TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER PART IIC: CONTROL OF STARTING MATERIALS

The materials listed below are tested for total aerobic microbial count to the limits shown and is negative for Salmonella, E. coli, Pseudomonas aeruginosa and Staphylococcus aureus.

Total Aerobic Count (Bacteria, Yeast, Mold) Does Not Exceed: (Colonies per Gram)

Microcrystalline Cellulose	100
Talc	500
Pregelatinized Starch (Maize)	1000
Hydroxypropyl Methylcellulose	1000
Magnesium Stearate	1000
Hydroxypropyl Cellulose LF	1000

2. Other Ingredients Not Described in a Pharmacopoeia Page C6, & Reference 4

a) Alcohol SD3A anhydrous [redacted] Satisfactory.

Identification Tests:
A. Ethanol-Conforms
B. Methanol-Conforms

Other Tests:
Solubility: Miscible with water to give clear solution.

[redacted]

[redacted]

b) OPACODE WB (Black)
OPACODE WB, NS-78-8001 (Black Iron Oxide) is tested to meet the following specifications:
Color Assessment: [redacted]
Fineness of Grind: [redacted]
Specific Gravity: [redacted]
Viscosity: [redacted]
Regulatory Information: Meets requirements listed in USP, F.C.C. or 21 C.F.R. for the intended use in Drugs and Cosmetics.

Satisfactory.

c) OPACODE WB (Red)
OPACODE WB, NS-78-1701 (Red Iron Oxide) is tested to meet the following specifications:
Color Assessment: [redacted]
Fineness of Grind: [redacted]
Specific Gravity: [redacted]
Viscosity: [redacted]
Regulatory Information: Meets requirements listed in USP, F.C.C. or 21 C.F.R. for the intended use in Drugs and Cosmetics.

Satisfactory.

Control of Starting Materials, Packaging Material (Immediate Packaging)

Specification and Routine Tests Pages C8-C10

Bottle Packs
Bottles are checked for correct appearance, absence of malformed and damaged items, incorrect design, cleanliness, lack of manufacturing waste, conformity to an IR identity test, and correct dimensions and weight. Bottle closures are checked for correct appearance, absence of damaged or malformed items, cleanliness, conformity to an IR identity test, correct dimensions and weight, and correct fit to the bottles.

Satisfactory.

[redacted]

FAMOTIDINE OTC FILM-COATED TABLETS	TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER PART IIC: CONTROL OF STARTING MATERIALS	
	Blister Packs The reels are checked for absence of damage and deformity, correct dimensions, core diameter, reel diameter, foil width and thickness, correct weight per linear meter, conformity to an IR identity test, and presence of the correct stock code number on the core.	Satisfactory.
	Aluminum Foil and Paper/Poly Pouches The reels are checked for absence of damage and deformity, correct dimensions, core diameter, reel diameter, foil width and thickness, correct weight per linear meter, conformity to an IR identity test, and presence of the correct stock code number on the core.	Satisfactory.

[redacted]

FAMOTIDINE OTC FILM-COATED TABLETS	TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER PART IIE: CONTROL TESTS ON THE FINISHED PRODUCT

Control Tests on the Finished Product Pages E1-E3, References 6-8.

Complies with USP monograph for Famotidine Tablets (see insert).

Product Specification and Control Methods

Specification based on those of Pepcid Tablets 20 mg & 40 mg.

General Product Characteristics:
A pale-rose (pink) colored, rounded-square, film-coated tablet with the Trademark printed on one side.

Identification Tests:
Same retention time as the standard on HPLC.
Alternately, has essentially the same RF as the standard on TLC examination.

Assay:
[redacted] of label claim at release and on control, using the HPLC method.

Satisfactory.

Purity Tests:

[redacted]

Satisfactory.
No related substances test in FPS for Pepcid Tablets 20 mg, 40 mg.

Pharmaceutical Tests:
Conforms to the EP and USP tests for dose uniformity, using the HPLC assay method.

Dissolution Tests:
Not less than 85% dissolved in 30 minutes, using the paddle apparatus at 50 rpm with 0.1M phosphate buffer (pH 4.5) at 37°C (tentative specification). Samples are analyzed by HPLC.

USP method.

Should include a test (and limit) for moisture content.

[redacted]

Famotidine Tablets

» Famotidine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_8H_{15}N_7O_2S_3$.

Packaging and storage—Preserve in well-closed, light-resistant containers.

Reference standard—*USP Famotidine Reference Standard*—Dry at a pressure between 1 mm and 5 mm of mercury at 80° for 5 hours before using.

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that of the *Standard preparation*, as obtained with *Assay*.

Dissolution ⟨711⟩—

Medium: pH 4.5, 0.1 *M* phosphate buffer; prepared by dissolving 13.6 g of monobasic potassium phosphate in one liter of water; 900 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Procedure—Determine the amount of $C_8H_{15}N_7O_2S_3$ dissolved from ultraviolet absorbances at the wavelength of maximum absorbance at about 265 nm using filtered portions of the solution under test, suitably diluted with *Dissolution Medium*, if necessary, in comparison with a *Standard solution* having a known concentration of USP Famotidine RS in the same medium.

Tolerances—Not less than 75% (*Q*) of the labeled amount of $C_8H_{15}N_7O_2S_3$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—

Buffer solution—Dissolve 1.36 g of monobasic potassium phosphate in 800 mL of water, and adjust to a pH of 7.0, determined potentiometrically, by the addition of 1 *N* sodium hydroxide with mixing. Dilute with water to 1000 mL, and mix.

Mobile phase—Prepare a mixture of water, methanol, and *Buffer solution* (31:6:3), adjust to a pH of 5.0, determined potentiometrically, by the addition of 0.1 *N* sodium hydroxide, mix, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—[NOTE—Prepare fresh daily.] Dissolve a suitable quantity of USP Famotidine RS in *Buffer solution* to obtain a solution having a known concentration of about 80 µg of famotidine per mL.

Assay preparation—Weigh and finely powder not less than 20 Famotidine Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 200 mg of famotidine, to a 500-mL volumetric flask. Add 50 mL of *Buffer solution* and 300 mL of water, sonicate for 5 minutes, and mechanically shake for 1 hour. Dilute with water to volume, mix, and filter. Quantitatively dilute a portion of the clear filtrate with *Buffer solution* to obtain a solution containing about 80 µg of famotidine per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L3. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure*: the capacity factor is not less than 4.0, the column efficiency, determined from the analyte peak, is not less than 3200 theoretical plates, the tailing factor for the famotidine peak is not more than 3.0, and the relative standard deviation for replicate injections is not more than 2.0%. [NOTE—When *System Suitability* cannot be achieved, the following wash sequence for the column may be used: wash with 0.05 *M* phosphoric acid at a flow rate of 1.3 mL per minute for 15 minutes, wash with water at a flow rate of 1.3 mL per minute for 15 minutes, wash with acetonitrile at a flow rate of 1.3 mL per minute for 15 minutes, wash with methanol at a flow rate of 1.3 mL per minute for 15 minutes, and finally precondition the column with *Mobile phase*.]

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_8H_{15}N_7O_2S_3$ in the portion of Tablets by the formula:

$$2.5C(r_U/r_S),$$

in which C is the concentration, in µg per mL, of USP Famotidine RS in the *Standard preparation*, and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Famotidine Tablets

Change to read:

Identification—

■**A:** (See *Thin-layer Chromatographic Identification Tests* ⟨201⟩.)

Developing solvent—Prepare a mixture of ethyl acetate, methanol, toluene, and ammonium hydroxide (40:25:20:2).

Standard solution—Dissolve USP Famotidine RS in glacial acetic acid to obtain a solution having a concentration of 4 mg per mL.

Test solution—Transfer a portion of finely powdered Tablets, equivalent to about 40 mg of famotidine, to a 10-mL volumetric flask. Dissolve in glacial acetic acid with the aid of sonication, dilute with glacial acetic acid to volume, and centrifuge to get a clear liquid.

Procedure—Apply separately 10 µL each of the *Standard solution* and the *Test solution* to a suitable thin-layer chromatographic plate coated with a 0.25-mm layer of chromatographic silica gel mixture, allow the spots to dry, and develop the plate in a paper-lined chromatographic chamber equilibrated with *Developing solvent* for about one hour prior to use. Allow the chromatogram to develop until the solvent front has moved about 15 cm. Remove the plate, air-dry, and examine the plate under short-wavelength ultraviolet light: the principal spot from the *Test solution* corresponds in appearance and R_f value to that of the *Standard solution*.

B:■ The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that of the *Standard preparation* as obtained in the *Assay*.

Change to read:

Assay—

Buffer solution—Dissolve 1.36 g of monobasic potassium phosphate in 800 mL of water, and adjust to a pH of 7.0, determined potentiometrically, by the addition of 1 *N* sodium hydroxide with mixing. Dilute with water to 1000 mL, and mix.

Mobile phase—Prepare a mixture of water, methanol, and *Buffer solution* (31:6:3), adjust to a pH of 5.0, determined potentiometrically, by the addition of ■phosphoric acid■, mix, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—[NOTE—Prepare fresh daily.] Dissolve a suitable quantity of USP Famotidine RS in *Buffer solution* to obtain a solution having a known concentration of about 80 µg of famotidine per mL.

Assay preparation—Weigh and finely powder not less than 20 Famotidine Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 200 mg of famotidine, to a 500-mL volumetric flask. Add 50 mL of *Buffer solution* and 300 mL of water, sonicate for 5 minutes, and shake by mechanical means for 1 hour. Dilute with water to volume, mix, and filter. Quantitatively dilute a portion of the clear filtrate with *Buffer solution* to obtain a solution containing about 80 µg of famotidine per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L3. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure*: the capacity factor is not less than 4.0, the column efficiency, determined from the analyte peak, is not less than 3200 theoretical plates, the tailing factor for the famotidine peak is not more than 3.0, and the relative standard deviation for replicate injections is not more than 2.0%. [NOTE—When *System Suitability* cannot be achieved, the following wash sequence for the column may be used: wash with 0.05 *M* phosphoric acid at a flow rate of 1.3 mL per minute for 15 minutes, wash with water at a flow rate of 1.3 mL per minute for 15 minutes, wash with acetonitrile at a flow rate of 1.3 mL per minute for 15 minutes, wash with methanol at a flow rate of 1.3 mL per minute for 15 minutes, and finally precondition the column with *Mobile phase*.]

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_8H_{15}N_7O_2S_3$ in the portion of Tablets taken by the formula:

$$2.5C(r_U/r_S),$$

in which C is the concentration, in µg per mL, of USP Famotidine RS in the *Standard preparation*, and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

FAMOTIDINE OTC FILM-COATED TABLETS	TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER PART IIE: CONTROL TESTS ON THE FINISHED PRODUCT

Identification and Determination of Excipient Page E5, Reference 10

[redacted]

Satisfactory.

Control Tests on the Finished Product - Scientific Data

Summary of Analytical Development and Validation Studies Pages E6-E78

The HPLC Method of Assay

[redacted]

Satisfactory data submitted.

[redacted]

FAMOTIDINE OTC FILM-COATED TABLETS	TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER PART IIE: CONTROL TESTS ON THE FINISHED PRODUCT

Analysis of Dissolution Rate

The dissolution testing is conducted in 0.1M phosphate buffer. Dissolution measurements are conducted using 900 mL of media using USP Apparatus II with paddles at 50 rpm. Sample concentrations are measured by the identical HPLC assay for the composite and dose uniformity assay testing.

Separate validation data for use in dissolution testing provided - satisfactory.

The determination of the amount of famotidine in 900 mL of dissolution media has been reported in previous MAA for the 20 mg and 40 mg famotidine tablets.

Batch Analyses Page E111

The results are given below for the analysis of 3 market-image batches manufactured by MRL in West Point, PA, U.S.A.

Satisfactory.

Note - this is not one of the sites proposed on form MLA 201 page 11.

[redacted]

FAMOTIDINE
OTC
FILM-COATED
TABLETS

TABULAR SUMMARIES
REFERRING TO PART II
OF THE DOSSIER

PART IIE: CONTROL TESTS
ON THE FINISHED PRODUCT

Famotidine Film-Coated Tablets, 10 mg Batch Analysis

		0208 FCT — - —
Lot Number		[redacted]
Date Manufactured		
Batch Size (tablets)		
Appearance	[Specification] Rounded-square film-coated, pale rose-colored tablet	
Famotidine Assay (mg/tab, % of claim)	[redacted] of claim	
Degradates	[redacted]	
Dose Uniformity (Mean, % RSD)	Conforms to USP	
Dissolution	Minimum 85% dissolved in 30 minutes (Q=80%)	
Identity	Behaves as authentic STD by HPLC	
Batch Type		

Batch Type: BS - Bioavailability Studies; SS - Stability Studies
ND = None Detected (limit of detection; A1, A2, A6 [redacted]

[redacted]

FAMOTIDINE OTC FILM-COATED TABLETS

TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER

PART IIF: STABILITY STUDIES

Stability Tests On Active Ingredients Pages F1 and F2

Stability indicating data for famotidine drug substance can be found in previous MAAs for famotidine products. This data indicates that solid famotidine is stable for at least three years at ambient temperature and humidity. Additional stability data is provided in Part IIF, Table F1, (Page F2). These results also indicate that solid famotidine is stable for at least 3 years at ambient temperature and humidity.

Checked as correct.

Stability Tests on the Finished Product

Batches Tested and Packaging Used Pages F4 and F5

Three batches of tablets were placed on stability in a variety of proposed market containers. Part II F, Table F2 (Page F5) of the dossier summarizes the 3 lots indicating the duration in weeks of the study for packaging configurations at the time of writing. Part IIF Tables F3-F9 (Pages F10-F18) provides a summary of the stability test results.

HDPE bottle with non-child resistant closure proposed. Use of non-child resistant closures undesirable.

Storage Conditions Page F6

The principle conditions used are 30°C/ambient relative humidity, 30°C/75% relative humidity; 40°C/ambient relative humidity, 40°C/75% relative humidity, and 50°C/ambient relative humidity.

Analytical Protocols and Methods Page F6

Tablets are being tested for appearance, famotidine content, dissolution and degradates using the test methods described in Part II E.1.1. (pages E1-E3) of the dossier.

[redacted]

FAMOTIDINE OTC FILM-COATED TABLETS	TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER

PART IIF: STABILITY STUDIES

Initial, three, and six-month stability assays for the 10 mg film-coated product were performed at Merck Research Laboratories, West Point, PA. Stability samples for the film-coated product have since been transferred to Lancaster Laboratories, Inc., 2425 New Holland Pike, Lancaster, PA, USA.

Stability Test Results Pages F7-F29

The famotidine tablets exhibit acceptable stability under ambient storage conditions. The stability of the market image product is consistent with stability data compiled on probe lots during the clinical phase of the stability program. Satisfactory assay and dissolution results were obtained.

Supports the proposed shelf-life.

The chemical stability of the final market image of famotidine tablets was also challenged using stressed conditions. Famotidine potency and degradate results enabled appropriate degradate specifications to be established to control the product through the expiry period.

Supportive data.

Famotidine dissolution remains unchanged when tablets are stored in market containers as long as 18 months at 30°C and ambient RH.

To substantiate the proposed expiration dating period of two years and recommended storage conditions, preliminary statistical analysis was performed on three lots. The data indicate that the stability is essentially independent of the container-closure system which supports the equivalency of the various proposed market packages. The preliminary data indicate slightly increased degradation when the product is exposed to elevated relative humidity which supports the "Protect From Moisture" label statement.

Finished product should also be controlled for moisture content.

[redacted]

FAMOTIDINE OTC FILM-COATED TABLETS	TABULAR SUMMARIES REFERRING TO PART II OF THE DOSSIER PART IIF: STABILITY STUDIES

Dissolution profiles of the market container stability studies for the three lots support the specification limits. To date, potency and degradate results collected on the three market container stability lots after 18 months storage at 30°C/ambient RH show there is little potency loss and an increase in total degradation of no more than 1%.

See inserts.

Conclusions

Overall, the results to date indicate that the tablets in the primary packages show acceptable stability with no changes of significance being seen.

Data supports a shelf life of 24 months; it is expected that as further data are accumulated, this life can be extended.

24 month self-life justified.

Further Stability Studies

Three early production lots manufactured will be placed on stability. The extension of the expiration dating period will be based upon full shelf-life data developed using the stability protocol. In addition, as for all Merck products, samples will be taken annually from normal production lots, held under ambient conditions, and tested at appropriate intervals.

[redacted]

Table F3 Stability Summary, Primary Containers - 30°C/Ambient Humidity

Container - Closure	*Batch No.*	*Time (wks)*	*% Claim*	*DEGRADATES A-1*	*A-2*	*A-3*	*A-6*	*Total*	*DISSOLUTION Ave*	*N*	*Min*	*Max*
HDPE-NCR	D001								98	18	96	100
HDPE-NCR	D001								103	6	102	105
HDPE-NCR	D001								100	6	98	102
HDPE-NCR	D001								98	6	97	100
HDPE-NCR	D001								98	6	97	98
HDPE-NCR	D002								99	11	95	104
HDPE-NCR	D002								102	6	101	103
HDPE-NCR	D002								100	6	100	101
HDPE-NCR	D002								100	6	98	102
HDPE-NCR	D003								99	12	95	103
HDPE-NCR	D003								101	6	99	102
HDPE-NCR	D003								100	6	99	101
HDPE-NCR	D003								98	6	97	100
HDPE-CR	D001								98	18	96	100
HDPE-CR	D001								102	6	101	103
HDPE-CR	D001								99	6	97	101
HDPE-CR	D001								98	6	98	100
HDPE-CR	D001								98	6	97	98
HDPE-CR	D002								99	11	95	104
HDPE-CR	D002								102	6	101	103
HDPE-CR	D002								101	6	100	102
HDPE-CR	D002								99	6	99	100
HDPE-CR	D003								99	12	95	103
HDPE-CR	D003								101	6	100	102
HDPE-CR	D003								99	6	98	101
HDPE-CR	D003								100	6	99	102
Foil Pouch-NCR1	D001								98	18	96	100
Foil Pouch-NCR1	D001								102	6	100	103
Foil Pouch-NCR1	D001								100	6	99	102
Foil Pouch-NCR1	D001								99	6	98	101
Foil Pouch-NCR1	D002								99	11	95	104
Foil Pouch-NCR1	D002								102	6	101	102
Foil Pouch-NCR1	D002								101	6	100	102
Foil Pouch-NCR1	D002								100	6	98	102
Foil Pouch-NCR1	D003								99	12	95	103
Foil Pouch-NCR1	D003								101	6	100	103
Foil Pouch-NCR1	D003								100	6	99	101
Foil Pouch-NCR1	D003								100	6	99	100

Table F3 (Cont.) Stability Summary, Primary Containers - 30°C/Ambient Humidity

Container · Closure	Batch No.	Time (wks)	% Claim	DEGRADATES A-1	A-2	A-3	A-6	Total	DISSOLUTION Ave	N	Min	Max
Paper Pouch-NCR	D001								98	18	96	100
Paper Pouch-NCR	D001								102	6	100	103
Paper Pouch-NCR	D001								99	12	97	101
Paper Pouch-NCR	D001								98	6	97	99
Paper Pouch-NCR	D001								99	6	98	99
Paper Pouch-NCR	D002								99	11	95	104
Paper Pouch-NCR	D002								102	6	101	103
Paper Pouch-NCR	D002								101	6	99	102
Paper Pouch-NCR	D002								99	6	96	100
Paper Pouch-NCR	D003								99	12	95	103
Paper Pouch-NCR	D003								101	6	100	103
Paper Pouch-NCR	D003								99	6	99	101
Paper Pouch-NCR	D003								98	6	97	100
PVC-CR	D001								98	18	96	100
PVC-CR	D001								101	6	100	103
PVC-CR	D001								99	6	98	101
PVC-CR	D001								97	6	96	98
PVC-CR	D001								97	6	96	97
PVC-CR	D002								99	11	95	104
PVC-CR	D002								102	6	101	103
PVC-CR	D002								99	6	97	100
PVC-CR	D002								99	6	98	101
PVC-CR	D003								99	12	95	103
PVC-CR	D003								101	6	99	102
PVC-CR	D003								99	6	99	100
PVC-CR	D003								99	6	98	102
PVC-NCR	D001								98	18	96	100
PVC-NCR	D001								101	6	100	103
PVC-NCR	D001								100	6	98	101
PVC-NCR	D001								98	6	97	98
PVC-NCR	D001								97	6	95	98
PVC-NCR	D002								99	11	95	104
PVC-NCR	D002								102	6	101	103
PVC-NCR	D002								100	6	99	102
PVC-NCR	D002								98	6	96	100
PVC-NCR	D003								99	12	95	103
PVC-NCR	D003								101	6	101	102
PVC-NCR	D003								100	6	98	101
PVC-NCR	D003								100	6	98	101

FAMOTIDINE OTC	EXPERT OPINION ON PART II OF THE DOSSIER

Information on the Author

[redacted]

FAMOTIDINE OTC	EXPERT OPINION ON PART II OF THE DOSSIER

[redacted]

[redacted]

PL 0025/0312-13 : Abridged PL Application

Blocazide 10 mg Tablets (Film-coated and Chewable)

Change of Legal Status : POM to P

Preclinical Assessment : [redacted] March 1993

Blocazide Tablets contain famotidine as active substance, one of the class of histamine antagonists acting specifically at H_2 receptor sites.

In this application to change the legal status, there is no new preclinical (or non-clinical) data. The existing preclinical safety base is summarised and commented upon in an abbreviated Expert Report (Appendix 1 - attached).

The conclusion is that nothing in this preclinical database raises concerns about the proposed change to self-medication. A full range of animal studies was undertaken and reported in support of the original PL application and these remain relevant and appropriate to allow the less-controlled use under P status. There are thus no preclinical reasons to oppose the grant of a change in legal status from POM to P for Blocazide 10 mg Tablet formulations.

Famotidine

[redacted]

Abbreviated Nonclinical Pharmacology and Toxicology Documentation

Introduction

Famotidine (MK-0208, YM-11170, L-643,341) is a highly potent gastric H_2-receptor antagonist. It inhibits gastric acid secretion and accelerates healing of peptic ulcers and is approved for the treatment of active gastric and duodenal ulcers and for maintenance therapy for duodenal ulcer patients. It has been marketed for these indications in many countries around the world for several years.

The nonclinical pharmacology of famotidine has been well characterized in several in vivo and in vitro systems. It has no significant effects on other major organ systems. The absorption, metabolism, and excretion of famotidine were studied in rats and dogs. It is well absorbed from the gastrointestinal tract and the only metabolite (sulfoxide) was present in minor amounts. These data have been submitted as part of preclinical data supporting oral and intravenous administration in man.

The safety of famotidine has been extensively evaluated in laboratory animals and in several in

Introduction (continued)

vitro systems and the detailed study reports have been submitted as part of the original application for marketing the tablet. No additional studies have been done since 1985. The objective of the present review is to briefly summarize prior preclinical information to support marketing of famotidine over the counter. The preclinical safety of famotidine is only briefly reviewed here. References to the respective sections of the original submission can easily be made. A full list of studies is attached (Attachment 1).

Single Dose Toxicity

Famotidine was found to be relatively non-toxic based on single dose toxicity studies in rats, mice, and dogs. The oral LD_{50} was greater than 8 g/kg and the LD_{50} by parenteral routes was greater than 254 mg/kg.

Repeated Dose Toxicity

Rats and dogs tolerated repeated-dose oral administration of famotidine for up to one year at doses up to 2 g/kg/day in rats and up to 1 g/kg/day in

Repeated Dose Toxicity (continued)

dogs. Intravenous administration was also well tolerated by rats for 13 weeks at dosage levels up to 20 mg/kg/day and by dogs, except for occasional emesis, at dosage levels up to 10 mg/kg/day for 26 weeks. In rat studies there was a dose- and time-dependent increase in the incidence and, to some extent, the severity of eosinophilic cytoplasmic granularity (ECG) of gastric chief cells compared to controls. Similar ECG of gastric chief cells had been seen in rats treated with compounds having similar pharmacologic activity and this change was fully reversible with discontinuation of treatment. A similar change has not been seen in mice or dogs. This change is considered to be of no toxicologic significance.

Developmental and Reproductive Toxicity

Famotidine was tested to assess its teratogenic potential in rats and rabbits and its effect on fertility and reproduction and peri- and postnatal development in rats. No alteration in reproductive

Developmental and Reproductive Toxicity (continued)

parameters and no evidence of teratogenicity were seen in rats and rabbits given high doses of famotidine by oral and intravenous routes. Fetotoxicity was seen but only at maternotoxic doses.

Genetic Toxicity

The results of extensive in vitro and in vivo studies using mammalian and non-mammalian systems indicates that there is no genotoxic risk associated with famotidine.

Carcinogenicity

Studies were performed in rats (106 weeks) and mice (92 weeks) at very high doses to evaluate the carcinogenic potential of famotidine. These studies did not indicate any treatment-related increased tumor incidence.

Special Toxicity

The safety of famotidine was tested with regard to its effects on the thyroid, eye, and injection site and immunogenic and hemolytic potential. These studies

Special Toxicity (continued)

did not show any effect on the thyroid of rats and no immunogenicity in mice or guinea pigs. Famotidine was non-irritating to the rabbit eye and intravenous injection site. Famotidine also did not cause hemolysis of human and rabbit erythrocytes.

Conclusion

The safety of famotidine has been extensively evaluated in in vivo studies in laboratory animals and in several in vitro studies at doses that are very high relative to the clinical dose. There are no findings of any toxicologic significance. Furthermore, famotidine as a prescription product has been used extensively for the treatment of active gastric and duodenal ulcers and as maintenance therapy for duodenal ulcer patients for several years. The dosages used were consistently higher than the dose which is being proposed for OTC use. There are no preclinical safety issues which would preclude the use of the compound as a self medication in the general population.

Famotidine OTC

Abbreviated Expert Report on the Nonclinical

Pharmacology and Toxicology Documentation

Famotidine (MK-0208, YM-11170 or L-643,341) is a widely used highly potent gastric H_2-antagonist. Famotidine tablets and an intravenous formulation have been approved for the treatment of active gastric and duodenal ulcers for several years. An application is now being submitted for over the counter (OTC) use of a lower dose famotidine tablet.

The original application included a full account of the preclinical data supporting the oral and intravenous administration. No further preclinical studies were done since the original submission. Therefore, this will be an abbreviated review of preclinical information.

The pharmacodynamics and pharmacokinetics of famotidine were studied using well accepted test systems. These pharmacodynamic studies showed that famotidine is a potent, competitive H_2-antagonist with little other pharmacologic action. The absorption, metabolism and excretion studies were done in the rat and dog. The drug is well absorbed orally and excreted predominantly in the urine as unchanged drug. There is no change in the metabolism or accumulation following repeated daily dosing.

The general toxicity of famotidine following single and repeated oral and intravenous dosing has been studied in several laboratory animal species. These studies employed well accepted study design with appropriate numbers of animals and evaluated multiple antemortem and postmortem parameters. The doses used in these studies were very large relative to the maximum intended clinical dose. Overall, famotidine had

a very low order of toxicity. This is evidenced by the very large oral LD_{50} (>8 g/kg) and by the lack of any significant toxicity in rats at doses up to 2000 mg/kg/day and in dogs at doses up to 1000 mg/kg/day for one year.

Extensive series of studies to assess the reproductive toxicity, genetic toxicity and carcinogenicity of famotidine were done using well accepted in vivo and in vitro studies. These studies clearly demonstrated that famotidine is not teratogenic, genotoxic or carcinogenic.

In conclusion, the safety of famotidine has been clearly established in preclinical studies. Furthermore, famotidine as a prescription product (oral and IV) has been used extensively for the treatment of active gastric and duodenal ulcers for many years. The doses used were consistently higher than the dose which is being proposed for OTC use. Therefore, no additional toxicity studies are needed prior to the projected human use as an OTC product. There are no preclinical issues which would preclude the use of the compound as a self medication in the general population.

ID1632/kmc

ABRIDGED APPLICATION PRE-ASSESSMENT CHECK LIST

To be completed by assessor who initiates assessment

Product Name: [redacted]	PL: [redacted]	
Application to be returned as invalid if any of the following criteria are not satisfied.	TICK BOX	
	YES	NO
MLA 201 Form for each dosage form and strength	✓	
Legibility (Dossiers should be bound and paginated)	✓	
Language (All data must be in English)	✓	
Expert Reports and CV's acceptable		
Pharmaceutical	✓	
Tox/Clinical	✓	
Supporting Data (Parts I-V) present	✓	
'Applicants Part' of DMF present (if required) for each active supplier	NA	
EC/65/65 Article 4.8(a)(iii) (If applicable, 10 year rule applies)	NA	
Additional Comment if Application is Invalid:		

ASSESSORS SIGNATURE [redacted] ..... **DATE:** [redacted]

GROUP MANAGER: ..... **DATE:** .....
(required only if application is invalid)

5A

GA/+7934L/MT/1

Department of Health

MEDICINES CONTROL AGENCY

Market Towers 1 Nine Elms Lane London SW8 5NQ

Telephone 071-273 0425 Room 1313
Facsimile 071-273 0323

MCA

[redacted]

[redacted]

Dear Sir/Madam

MEDICINES ACT 1968: LICENSING
PRODUCT LICENCE APPLICATION NO [redacted]

With reference to your application dated [redacted] for the grant
of a product licence in respect of [redacted]

the licensing authority requires the production of the undertakings and declaration referred to in Section 19(3) of the Medicines Act 1968. I should be pleased if you would arrange for these to be given by the manufacturer of the medicinal product. Forms for this purpose are enclosed. Only one need be completed. One relates solely to the current application. The other headed 'Omnibus' covers the current application or any future application involving the same manufacturer.

Yours faithfully

[redacted]

[redacted]

VALIDATIO[redacted]
MEDICINES CONTROL AGENCY ABRIDGED APPLICATIONS (NA)(01)(31/01/93)

NO. & CO. : PL 00025/0312
MERCK SHARP & DOHME LTD [redacted]

DATE RECEIVED : 27/01/93
DATE REGISTERED : 27/01/93
DATE FEE PAID : 27/01/93
DATE NOTIFIED TO REG'N : 27/01/93
REC'D IN VALID'N : 29/01/93
VALIDATION DATE : 29/01/93

MANUFACTURER : F WOELM PHARMA GMBH, MAX-WOELM-STRASSE, 3440 ESCHWEGE, GERMANY.

MERCK SHARP & DOHME LTD, SHOTTON LANE, CRAMLINGTON, NORTHUMBERLAND NE 23 9JU

F MERCK SHARP & DOHME (ITALIA) SPA, VIA EMILIA 21,27100 PAVIA,ITALY

PRODUCT NAME : **BLOCAZIDE 10MG TABLETS (FILM-COATED)**

PHARMACEUTICAL FORM : FILM COATED TABLETS

PACK SIZE(S) : 2, 6, 10, 12, 18, 20, 30, 40, 50

LEGAL STATUS REQUESTED : PHARMACY SALE ONLY **METHOD OF SALE** : REGISTERED PHARMACIES

ACTIVE CONSTITUENTS : **FAMOTIDINE** USP 010.0 MG
F YAMANOUCHI IRELAND CO LTD DUBLIN EIRE
F YAMANOUCHI PHARM CO LTD TOKYO JAPAN

THERAPEUTIC CODE(S) : A30

DRUG SUBSTANCE DETAIL : USP SPECIFICATION. SEE PL 00025/0215-6 (g.8/9/87) Pepcid Tablets 20mg and 40mg.

CLINICAL USE : TREATMENT OF INDIGESTION, ACID INDIGESTION, NERVOUS INDIGESTION, HEARTBURN, DYSPEPSIA, ACIDITY, SYMPTOMS OF UPSET STOMACH ASSOCIATED WITH THESE CONDITIONS.

ROUTE OF ADMINISTRATION : ORAL

DOSAGE : ADULTS AND CHILDREN OVER 12 YEARS:- DOSAGE INTERVAL: AS NEEDED TO RELIEVE SYMPTOMS OR ONE HOUR BEFORE EATING FOR SYMPTOMS ASSOCIATED WITH FOOD AND BEVERAGE. MAXIMUM INTAKE IN 24 HOURS IS 20MG.

SUPPORTING DATA : MLA 201, EXPERT REPORTS, ABRIDGED CHEMISTRY & PHARMACY 2 VOL(S), TOX & PHARM DOC 1 VOL(S), CLINICAL DOC 13 VOL(S).

NOTES & BACKGROUND : 1. Application coming in with full data as a POM to P application for a 10mg film-coated tablet.

2. Applicant holds PL 00025/0215-6 (g.8/9/87) Pepcid Tablets 20mg and 40mg.

3. Records show that both AIM's have been used in previously granted licences.

INFORMATION SECTION : CONTACT INFORMATION ROOM ON ASSESSMENT.

OTHER INFORMATION : AAC FEE : £17800

POM TO P

SERIAL NUMBER : 81563 VALIDATOR [redacted]

COMMITTEE DEADLINE :30/05/93 MEDICAL ASSESSOR : PHARMACEUTICAL ASSESSOR : ROUTE :

[redacted]

Department of Health

MEDICINES CONTROL AGENCY

Market Towers 1 Nine Elms Lane London SW8 5NQ

Telephone 071-273 0677/0678

Facsimile 071-273

[redacted]

[redacted]

[redacted]

Dear [redacted]

APPLICATION FOR A PRODUCT LICENCE
PRODUCT: [redacted]

Thank you for your application for a product licence dated [redacted] which was received on 27/1/93.

Please quote the following reference in all future correspondence: [redacted].

You are advised that under the Medicines Act 1968 it is unlawful to market the product until the licence is granted.

Yours faithfully

[redacted]

REGISTRATION SECTION

0025/0312

Medical Department

[redacted]

VIA COURIER

MG/DLGC - S:JAN93.116

27 JAN 1993

27 January 1993

The Registration Section
Department of Health
Medicines Division
Third Floor
Britannia House
7 Trinity Street
LONDON SE1 1DA

Dear Sir/Madam

ABRIDGED PRODUCT LICENCE APPLICATION:
BLOCAZIDE TABLETS (FILM-COATED AND CHEWABLE), PL 0025/0312-0313
POM TO P APPLICATION

I hereby wish to make a POM to P application for BLOCAZIDE Tablets (Famotidine, MSD). Famotidine tablets are already marketed in the UK as a prescription only medicine in strengths of 20 and 40 mg tablets. We now wish to introduce as a pharmacy only medicine Famotidine tablets as a 10 mg film-coated and chewable tablet, under the tradename 'BLOCAZIDE'.

I would like to point out that this application is actually being submitted ahead of the Medicines Control Agency deadline of 31 January 1993, in accordance with MAL 77.

In support of this application, therefore, I enclose the following documentation in triplicate:

Part I: Product Particulars, Expert Opinoins
(in grey covers), 1 volume

Part II: Chemical and Pharmaceutical Documentation
(in red covers), 2 volumes

Part III: Toxicological and Pharmacological Documentation
(in green covers), 1 volume

Part IVA: Clinical Pharmacology
(in blue covers), 1 volume

Part IVB: Clinical Experience
(in blue covers), 10 volumes

The Registration Section
ABRIDGED PRODUCT LICENCE APPLICATION:
BLOCAZIDE TABLETS (FILM-COATED AND CHEWABLE), PL 0025/0312-0313
POM TO P APPLICATION

Part IVQ: Other information
(in blue covers), 2 volumes

Part V: Product Particulars
(in grey covers), 1 volume

Additionally a Part I can be found at the front of each summary volume of each part and Part V can be found at the back of each summary volume.

I also enclose:

One unbound copy of the Expert Opinion Reports.

Two unbound copies of the Form MLA 201 for each tablet formulation.

A data identification form

A copy of the letter sent to [redacted] with the payment for this application.

I hope that everything is satisfactory, however should you have any queries or questions, please contact me straight away.

Yours sincerely

[redacted]

Encs

cc: [redacted]

PRODUCT LICENCE NUMBER (if known) PL [redacted]

DATA IDENTIFICATION

To assist in the speedy processing of your application please indicate for which purpose you are submitting data.

PLEASE TICK RELEVANT BOX

CPMP MULTI-APPLICATION (INCOMING)	Application to be considered by the Committee for Proprietary Medicinal Products (CPMP)	
COPY OF CPMP OUTGOING MULTI-STATE APPLICATION	Copy of data on product already licensed in UK, to be linked with earlier data. Data to be used to apply in other EC Member states via the CPMP	
HIGH TECHNOLOGY/ BIOTECHNOLOGY APPLICATION	Product claimed as qualifying under List A or List B of Annex to Directive 87/22/EEC. For entering into CPMP 'Community Concertation' procedure.	
MAJOR	New Active Substance application (other than high technology/biotechnology product)	
ABRIDGED APPLICATION	Application for a product licence based on an established active drug substance	✓
VARIATION	To support a requested change in an existing PL or PLR	
ADDITIONAL DATA	To support a previous application. Data requested by (Name of officer/committee and date of request)	
APPEAL DATA	To support appeal against Section 21(1) or Section 21(3) letters issued by a committee	
OTHER	[redacted]	✓

[redacted]

[redacted]

Medical Department

[redacted]
Director

VIA COURIER

DLGC - S:JAN93.115

27 JAN 1993

27 January 1993

[redacted]
Finance Directorate
Medicines Control Agency
Department of Health
Market Towers
1 Nine Elms Lane
LONDON SW8 5NQ

cc: Registration Section, Britannia House
[redacted]

Dear Ms [redacted]

PL 0025/0312-0313, BLOCAZIDE TABLETS - ABRIDGED PRODUCT LICENCE APPLICATION

Please find enclosed a cheque for £25,185.00 for our Abridged Product Licence Application for BLOCAZIDE Tablets, bearing the PL Nos 0025/0312-0313. The application is for two formulations of the product; film-coated and chewable tablets.

As discussed with you previously, the fee enclosed is was calculated on the following basis:

One formulation at the complex abridged rate	£17,800.00
Second formulation at the standard abridged rate	£ 7,385.00
Total	**£25,185.00**

Also enclosed are a) an acknowledgement of receipt form; please would you complete and return it to me in the reply-paid envelope provided, and b) a copy of the letter that accompanied the application to the Registration section at Britannia House - this is really for your information more than anything else.

I trust that all is clear and look forward to receiving the completed acknowledgement form.

Yours sincerely

[redacted]
Regulatory Affairs Department

[redacted] [redacted]

APPLICATION FOR A PRODUCT LICENCE

MEDICINES ACT 1968, 1971, EEC 65/65

The Notes for Guidance will be helpful in completing this form - See Annex 1 attached

1 Name of Product

Please state pharmaceutical form and strength as well as name, eg, TABLETS 10 mg or INJECTION 10 mg/ml

BLOCAZIDE 10 mg
(Film-coated Tablets)

2 PL number allocated by LA: **PL 0025/0312**

3 Full name and address of the proposed licence holder: **Merck Sharp & Dohme Limited**
Hertford Road, Hoddesdon, Herts., EN11 9BU

4 Trading style to be shown on licence if different from above: —

5 Role of proposed licence holder: *(please tick in appropriate box(es))*

☑ (i) as person responsible for composition of product manufactured in UK,

☑ (ii) in the case of a proprietary medicinal product, as person responsible for placing it on the UK market,

☑ (iii) as person who imports or procures its importation,

☑ (iv) as person who first sells or supplies it as a medicinal product.

6 Activities for which licence is required: *(please tick in appropriate box(es))*

☑ (i) selling or supplying product in the UK,

☑ (ii) procuring the manufacture or assembly of the product for sale or supply in the UK,

☑ (iii) importing or procuring the importation of the product,

☑ (iv) Other (specify) [redacted]

7 Applicants own reference number: BLOCAZ/FIL

8 Details of earlier applications: *Please attach as an appendix.*

SEE APPENDIX

Appendix

Details of Earlier Applications

Clinical Trial Certificate (CTC 0025/0186): Oral
Granted 18 October 1983; last renewed October 1991.

Clinical Trial Exemption (CTX 0025/0225A): Intravenous Injection
Granted 11 November 1986; last renewed 8 March 1990.

Product Licence Applications (PL 0025/0215-0216):
PEPCID 20 mg and 40 mg Tablets
Granted 8 September 1987.

Abridged Product Licence Application (PL 0025/0246):
PEPCID PM Oral Suspension 40 mg/5 ml
Submitted 30 January 1990.

Abridged Product Licence Application
Additional Indication: Treatment of gastro-oesophageal reflux disease
(approved under Product Licence numbers PL 0025/0215-0216)
Approved 10 September 1991.

Abridged Product Licence Application (PL 0025/0286)
PEPCID Intravenous Injection 20 mg
Submitted 31 January 1992.

9 Scientific Evidence:

(i) Chemical and pharmaceutical documentation	Number of volumes	[redacted]	Number of pages	[redacted]
(ii) Toxicological and pharmacological documentation	Number of volumes	[redacted]	Number of pages	
(iii) Clinical documentation	Number of volumes		Number of pages	

To assist determination of the route of assessment and the fees payable, it would be helpful if you would complete the following sections 10, 11, 12 and 13 by indicating YES or NO as applicable, or ticking the appropriate box(es). See also guidance notes on completion of the MLA form.

10 Type of Application

Is this:

a. a new active substance?	~~YES~~/NO	l. a new indication for the active constituent(s)?	YES/~~NO~~
b. a product of high technology*?	~~YES~~/NO	m. made using novel excipient(s)?	~~YES~~/NO
c. a biological product?	~~YES~~/NO	n. a sterile product?	~~YES~~/NO
d. a product of biotechnology*?	~~YES~~/NO	o. in a container using novel material not previously used for this active substance?	~~YES~~/NO
e. a new salt or ester of a known active substance?	~~YES~~/NO	p. for a new target population for this active substance?	YES/~~NO~~
f. a novel delivery system?	~~YES~~/NO	q. for a new route of synthesis?	~~YES~~/NO
g. a new route of administration for this active substance?	~~YES~~/NO	r. for a new source or supplier for this active substance?	~~YES~~/NO
h. a surgical material?	~~YES~~/NO	s. has this method of sterilisation been used previously for this active substance?	~~YES~~/NO [redacted]
i. for use with contact lenses?	~~YES~~/NO	t. a sustained release product?	~~YES~~/NO
j. a new combination of known active substances?	~~YES~~/NO		
k. a cross-referral with the licence holder's approval to an already licensed PL? State number of PL	~~YES~~/NO		

11 Fees Payable

- ☐ Major (NAS)
- ☐ Major (NAS) orphan drugs

Abridged: indicate which type:

- ☑ Complex abridged
- ☐ Standard abridged
- ☐ Simple abridged

OFFICIAL USE ONLY

Fee to be checked by validation pharmacist

CORRECT YES/NO

Initialled: _____

Date: _____

If NO, please state the appropriate

FEE PAYABLE: _____

12 Are you applying for marketing authorisation using:

a. The EC concertation procedure?	~~YES~~/NO
b. The EC Multi-State procedure?	~~YES~~/NO

Route (a) is available only for products of BIOTECHNOLOGY or HIGH TECHNOLOG Y* whereas for route (b) the applicant must hold a licence in at least one Community Country and intend t o apply in at least two others.*

**See Guidance notes 3. (i) page 1 (Annex 1)*

13

Only if your answer under 12b is Yes complete this section

a. EC countries in which a marketing Authorisation is held:

b. Marketing Authorisation number(s) with Country of origin and dates of grant:

14

Only complete the following sections if your application is submitted without the complete results of pharmacological and toxicological tests or clinical trials as allowed under Article 4.8(a) of Directive 65/65/EEC - See 9 (ii) and (iii) above. If no data is supplied under 9(ii) and 9(iii) or only partial data, then complete 14, 15, 16.

Please indicate under which sub-section of the Article your application is made:

(ie 4.8(a)(i), (ii) or (iii)):

15

(a) Are you asking the Authority to make use of the originator's data and/or a Drug Master File in support of your application? YES/~~NO~~

(b) If YES, please give details and supply authorisation:

REFERENCE MAY BE MADE WHERE NECESSARY TO THE ORIGINAL PRODUCT LICENCE APPLICATION FOR PEPCID TABLETS (PL 0025/0215-0216) SUBMITTED BY MSD; GRANTED 8 SEPTEMBER 1987.

Where your answer to question 14 is (i) or (iii)
Give details of essentially similar product:

(c) Name:

(d) Manufacturer:

(e) (i) Country of 1st Authorisation:

(ii) Has it been authorised in the UK? YES/NO

Where the originator has not consented to use of the original data (ie, where your application is made under 4.8(a)(iii), supply:

(f) Date of first authorisation in the EC of the originator's product (this must be the same pharmaceutical form and dose as your application):

(g) Is this product marketed in the UK? YES/NO

(h) If the answer to (e) is Yes, state the PL number(s) in the UK:

16

Do you wish the licence to cover sale and supply of essential test batches of the product manufactured before the grant of the licence which meet the final specification approved by the Licensing Authority? YES/~~NO~~

17

Do you give your consent to the disclosure to the British Pharmacopoeia Commission of any information given in or in connection with this application and relating to pharmaceutical standards applicable to this product or its active ingredient(s) on the understanding that such information will not be used in the compilation of a monograph in the British Pharmacopoeia without prior reference to you? YES/NO

18

I/We apply for the grant of a product licence to the proposed holder named above in respect of the product(s) to which the Product Particulars in Part 1A refer, and in accordance with the other particulars annexed; the said licence to be for a period of five years and subject to the following provisions:

18.1 All the Standard Provisions applicable to product licences under regulations for the time being in force under Section 47 of The Medicines Act 1968.

18.2 The product shall not be recommended to be used for any purpose other than those specified in the Product Particulars as Uses, and shall be sold or supplied in accordance with the said Product Particulars except in so far as may from time to time be approved by the licensing authority.

18.3 The specification of the constituents and of the finished product shall be in accordance with the information contained in or furnished in connection with the application.

18.4 The product is to be manufactured only in accordance with the methods set out in this application or furnished in connection with it.

18.5 No material information has been omitted (within the knowledge of the signatory).

Date: [redacted]

Signature [redacted]

State capacity in which signed: [redacted]

Tel: [redacted] Extn: [redacted]

Name and address for communications (if different from 4):

FOR OFFICIAL USE ONLY

Should the licence application be withdrawn, please complete the following section in order to determine the percentage of the fee which may be rebated.

State below the fee on application - see page 1B Question 11:

Was this fee submitted by the applicant? YES/NO

Application withdrawn? YES/NO

If the answer is Yes, please indicate the stage of medical/ pharmaceutical or scientific assessment reached by ticking the appropriate box:

Not commenced	☐	Section 44 letter sent to applicant	☐
Commenced/ Not Completed	☐	Seen by S.4 Committee and/or Medicines Committee	☐
Completed	☐		

A 1 / /

Form MLA 201

PRODUCT PARTICULARS - a complete set of pages should be included for each strength of product

PL Number of Product: (Official use only)

/

1. Name of Product and Strength: *BLOCAZIDE 10 MG*

(Official use only)

2. Full description of Pharmaceutical form (eg tablets, slow-release tablets, capsules etc):

FILM-COATED TABLET FOR ORAL ADMINISTRATION TO HUMAN BEINGS.

(Official use only)

[redacted]

(Official use only)

3a. Legal status requested (please tick in appropriate box)

(Official use only)

Prescription		Pharmacy	X	General Sales		Not Applicable	

3b. Method of retail sale or supply: *FOR SUPPLY TO MEMBERS OF THE GENERAL PUBLIC THROUGH REGISTERED PHARMACIES, UNDER THE SUPERVISION OF A PHARMACIST.*

(Official use only)

Text should be completed in block capitals

Date: *24 JANUARY 1993*

(Official Use Only)

D	1						/										

4. Active Constituents

(Official use only)	Name	Specification Reference			Quantity/Dose Unit or % quantity					Unit	
	FAMOTIDINE	*U*	*S*	*P*		*1*	*0 • 0*			*M*	*G*
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				
							•				

Details of any overages:- these should not be included in the Formulation Columns but stated in this section.

1) Please enter constituent(s) as actual substances included in the formulation, eg. as salt and then as base equivalent where applicable.

2) See page E1, paragraph 2 for approved abbreviations

Where a Specification does not refer to the latest published monograph, the relevant year should be included in the Name Column and set in the Specification Reference Column. Where an ingredient has no official monograph please enter HSE in the Specification Reference Column.

3) In the case of liquid preparations: all quantities for oral preparations should relate to a 5 ml dosage. Please state in dosage information any deviation from this rule. Quantity should be expressed as a percentage for other liquid preparations, including parenterals please insert WW, WV etc as appropriate in the Unit Column. DO NOT INSERT a percentage sign, this is automatically inserted by computer.

4) The following abbreviations for units are recommended:-
NG nanogrammes; UG microgrammes; MG milligrammes; GM grammes; KG kilogrammes; UL microlitres; ML millilitres; L litres; U units (u); KU kilounits (1,000 u); MU megaunits (1,000,000 u); I.U. international units; UC microcuries; BC becquerels.

5) Trailing zeros following the decimal point may be omitted eg. 10.02 mg will suffice.

6) Please photocopy page if more space for constituents is required.

Date: *24 JANUARY 1993*

C 1 /

5. Recommended clinical indications and route(s) of administration

TREATMENT OF:

- *INDIGESTION*
- *ACID INDIGESTION*
- *NERVOUS INDIGESTION*
- *HEARTBURN*
- *DYSPEPSIA*
- *ACIDITY*
- *SYMPTOMS OF UPSET STOMACH ASSOCIATED WITH THESE CONDITIONS*

ROUTE OF ADMINISTRATION: ORAL

(Official use only)

All entries must be made in full. Cross references, eg. to accompanying data sheets are not acceptable.

Date: *24 JANUARY 1993*

B	1						/										

6. Recommended doses and dosage schedules:

Distinguish between adults, children and the elderly and between different clinical indications

(Official Use Only)

ADULTS AND CHILDREN 12 YEARS OF AGE OR OLDER:
DOSAGE: 10 MG.

DOSAGE INTERVAL: AS NEEDED TO RELIEVE SYMPTOMS OR ONE HOUR BEFORE EATING FOR SYMPTOMS ASSOCIATED WITH FOOD AND BEVERAGE.

MAXIMUM INTAKE IN 24 HOURS: 20 MG.

NO DOSAGE ADJUSTMENT IS NECESSARY FOR THE ELDERLY.

(Official use only)

Date: *24 JANUARY 1993*

B 2 /

7. Contraindications, Precautions and Warnings listed, with titles. In the following order:-

a) Contraindications
b) Interactions with other medicaments and other forms of interaction
c) Effects on ability to drive and to use machines
d) Other undesirable effects (frequency and seriousness)
e) Use in pregnancy and lactation
f) Other special warnings and precautions
g) Overdose (symptoms, emergency procedures, antidotes)
h) Incompatibilities (major)

A) CONTRAINDICATIONS

HYPERSENSITIVITY TO ANY COMPONENT OF THIS PRODUCT.

B) INTERACTIONS WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION

NO DRUG INTERACTIONS OF CLINICAL IMPORTANCE HAVE BEEN IDENTIFIED. 'BLOCAZIDE' DOES NOT INTERACT WITH THE CYTOCHROME P450-LINKED DRUG METABOLIZING ENZYME SYSTEM. COMPOUNDS METABOLIZED BY THIS SYSTEM WHICH HAVE BEEN TESTED IN MAN HAVE INCLUDED WARFARIN, THEOPHYLLINE, PHENYTOIN, DIAZEPAM, PROPRANOLOL, AMINOPYRINE AND ANTIPYRINE. INDOCYANINE GREEN AS AN INDEX OF HEPATIC BLOOD FLOW AND/OR HEPATIC DRUG EXTRACTION HAS BEEN TESTED AND NO SIGNIFICANT EFFECTS HAVE BEEN FOUND.

CONCOMITANT USE OF ALUMINIUM HYDROXIDE/MAGNESIUM HYDROXIDE DOES NOT INFLUENCE THE PHARMACODYNAMICS OR BIOAVAILABILITY OF 'BLOCAZIDE'.

'BLOCAZIDE' DOES NOT AFFECT BLOOD ALCOHOL LEVELS FOLLOWING ORAL INGESTION OF ETHANOL.

C) EFFECTS ON ABILITY TO DRIVE AND OPERATE MACHINERY

NONE KNOWN.

D) OTHER UNDESIRABLE EFFECTS (FREQUENCY AND SERIOUSNESS)

'BLOCAZIDE' HAS BEEN DEMONSTRATED TO BE GENERALLY WELL-TOLERATED. SIDE EFFECTS REPORTED IN $\geq$1% OF PATIENTS WERE HEADACHE AND DIZZINESS. THESE OCCURRED WITH COMPARABLE FREQUENCY IN PATIENTS TREATED WITH PLACEBO.

E) USE IN PREGNANCY AND LACTATION

CLINICAL TRIALS IN PREGNANT WOMEN HAVE NOT BEEN PERFORMED. AS WITH MOST MEDICINES, 'BLOCAZIDE' IS NOT RECOMMENDED FOR USE IN PREGNANCY, AND SHOULD BE USED ONLY UNDER THE ADVICE OF A PHYSICIAN.

FAMOTIDINE IS DETECTABLE IN HUMAN MILK. NURSING MOTHERS SHOULD NOT TAKE THIS DRUG OR SHOULD STOP NURSING.

(Official use only)

Date: *24 JANUARY 1993*

B 2 / /

7. Contraindications, Precautions and Warnings listed, with titles. In the following order:-

a) Contraindications
b) Interactions with other medicaments and other forms of interaction
c) Effects on ability to drive and to use machines
d) Other undesirable effects (frequency and seriousness)
e) Use in pregnancy and lactation
f) Other special warnings and precautions
g) Overdose (symptoms, emergency procedures, antidotes)
h) Incompatibilities (major)

E) *USE IN PREGNANCY AND LACTATION (CONTINUED)*

REPRODUCTIVE STUDIES HAVE BEEN PERFORMED IN RATS AND RABBITS AT ORAL DOSES OF UP TO 2000 AND 500 MG/KG/DAY, RESPECTIVELY (APPROXIMATELY 5000 AND 1250 TIMES THE MAXIMUM RECOMMENDED HUMAN DOSE, RESPECTIVELY), AND HAVE REVEALED NO EVIDENCE OF IMPAIRED FERTILITY OR HARM TO THE FETUS DUE TO FAMOTIDINE.

IN STUDIES WITH RATS GIVEN ORAL DOSES OF UP TO 2000 MG/KG/DAY OR INTRAVENOUS DOSES OF 200 MG/KG/DAY (APPROXIMATELY 5000 AND 500 TIMES THE MAXIMUM RECOMMENDED HUMAN DOSE, RESPECTIVELY), FERTILITY AND REPRODUCTIVE PERFORMANCE WERE NOT AFFECTED.

F) *OTHER SPECIAL WARNINGS AND PRECAUTIONS*

IN CLINICAL TRIALS, PATIENTS WITH OTHER UNDERLYING ACID GASTROINTESTINAL DISEASES (EG, DUODENAL ULCER, GASTRIC ULCER) DID NOT EXPERIENCE COMPLICATIONS; IN GENERAL, THEY DID NOT EXHIBIT A CLINICALLY SIGNIFICANT DETERIORATION IN THEIR CONDITION. HOWEVER, IF PATIENTS HAVE DIFFICULTY SWALLOWING OR ABDOMINAL DISCOMFORT PERSISTS THE UNDERLYING CAUSE SHOULD BE DETERMINED.

THERAPY SHOULD NOT EXCEED TWO WEEKS WITHOUT MEDICAL CONSULTATION.

WHEN 'BLOCAZIDE' WAS ADMINISTERED TO ELDERLY PATIENTS IN CLINICAL TRIALS, NO INCREASE IN THE INCIDENCE OR CHANGE IN THE TYPE OF DRUG-RELATED SIDE EFFECTS WAS OBSERVED.

G) *OVERDOSE*

PATIENTS HAVE TOLERATED DOSES UP TO 800 MG/DAY FOR MORE THAN A YEAR WITHOUT DEVELOPMENT OF SIGNIFICANT SIDE EFFECTS.

H) *INCOMPATIBILITIES*

NONE.

(Official use only)

Date: *24 JANUARY 1993*

E	1						/										

8. Other Constituents

(Official use only)	Name	Specification Reference			mod	Quantity/Dose Unit or % quantity	Unit	
	TABLET CORE:				[redacted]	[redacted]		
	MAGNESIUM STEARATE	*E*	*P*				*M*	*G*
	MICROCRYSTALLINE CELLULOSE	*E*	*P*				*M*	*G*
	PREGELATINISED MAIZE STARCH	*B*	*P*				*M*	*G*
	TALC	*E*	*P*				*M*	*G*
	INDUSTRIAL METHYLATED SPIRIT (OR ALCOHOL 95%	*B* *U*	*P* *S*	*P)*				
	PURIFIED WATER	*E*	*P*					
	TABLET COAT:							
	HYDROXYPROPYL-CELLULOSE	*E*	*P*				*M*	*G*
	METHYLHYDROXY-PROPYLCELLULOSE	*E*	*P*				*M*	*G*
	RED IRON OXIDE E172	*E*	*E*	*C*			*M*	*G*
	TALC	*E*	*P*				*M*	*G*
	TITANIUM DIOXIDE E171	*E*	*P*				*M*	*G*
	PURIFIED WATER	*E*	*P*					

1) Please leave a line between different components of the dosage form, eg. for capsule shell components, coating components.
2) Where a specification reference does not refer to the latest published monograph, the relevant year should be included in the Name Column and not in the Specification Reference Column. Where an ingredient has no official monograph please enter HSE in the Specification Reference Column. Abbreviations to be used for specification are:- BP, EP, BPC, BNF, USP, NF, FRP, DAB, IP, NDP, JAP, PHV, BHP.
3) Please complete modifier column marked MOD as follows:
   Insert TO if final volume cannot be expressed as a complete quantity.
   Insert ND for substances not detectable in the final formulation, eg. solvents.
   Insert QS if quantity not fixed eg. for substances used to adjust pH.
4) Recommended abbreviations for units are given on page D1, paragraph 4.
5) In the case of liquid preparations: all quantities for oral preparations should relate to a 5 ml dosage. Please state in dosage information any deviation from this rule. Quantity should be expressed as a percentage for other liquid preparations, including parenterals please insert WW, WV etc as appropriate in the Unit Column. DO NOT INSERT a percentage sign, this is automatically inserted by computer.
6) Trailing zero's following the decimal point may be omitted eg. 10.02 mg will suffice.
7) Please photocopy page if more space for constituents is required.

Date: *24 JANUARY 1993*

H	1						/										

9. Description of essential processes in the manufacture:

FAMOTIDINE, MICROCRYSTALLINE CELLULOSE, AND PREGELATINISED MAIZE STARCH ARE GRANULATED WITH A WATER/ETHANOL MIXTURE, DRIED, MILLED, LUBRICATED WITH MAGNESIUM STEARATE AND TALC, AND COMPRESSED INTO TABLETS.

THE TABLET COATING SUSPENSION IS PREPARED BY DISPERSING THE METHYLHYDROXYPROPYL-CELLULOSE AND HYDROXYPROPYLCELLULOSE IN THE PURIFIED WATER AND THEN DISPERSING THE TITANIUM DIOXIDE, TALC AND RED IRON OXIDE IN THIS SOLUTION. THE SUSPENSION IS SPRAYED ON THE COMPRESSED TABLETS IN A STANDARD COATING PAN.

10. Finished Product Specification:

APPEARANCE:	*PALE-ROSE (PINK), ROUNDED-SQUARE, FILM-COATED TABLET WITH THE TRADEMARK PRINTED ON ONE SIDE.*
IDENTITY:	*CONFIRMED BY HPLC (OR ALTERNATIVE TLC METHOD).*
FAMOTIDINE ASSAY:	[redacted] *OF LABEL CLAIM.*
DEGRADATES:	[redacted]
UNIFORMITY OF CONTENT:	*MEETS THE EP/USP SPECIFICATION.*
DISSOLUTION:	*A MINIMUM OF 85% OF THE LABEL CLAIM DISSOLVED IN 30 MINUTES.*

Date: *24 JANUARY 1993*

G 1 [ ][ ][ ][ ][ ][/][ ][ ][ ][ ][ ][ ][ ][ ][ ][ ]

11. Arrangements for storage and address(es) of storage premises:

BULK TABLETS WILL BE STORED BRIEFLY AT THE SITE OF MANUFACTURE AND THE SITE OF ASSEMBLY. FINISHED PRODUCT WILL BE STORED BRIEFLY AT THE SITE OF ASSEMBLY, AND FOR DISTRIBUTION AT MSD, CRAMLINGTON, UK.

12. Special precautions for storage:

STORE BELOW 30°C; PROTECT FROM MOISTURE.

13. Nature of container and closure | Shelf-life (A) | Shelf-life (B) | Pack Size

Nature of container and closure	Shelf-life (A)	Shelf-life (B)	Pack Size
OPAQUE HDPE BOTTLES WITH LDPE CLOSURES.	*24M*		*30*
			40
			50

Unit

Notes: 1) Shelf-life should be expressed in months (M), weeks (W) or days (D) as appropriate eg 3 6 M
A = Unopened.
B = After reconstitution or when the container is opened for the first time, if appropriate.

2) The pack size should contain numbers only, right aligned. If a decimal point is required it should occupy one box.

3) Where applicable enter the unit of measure as MG, GM, ML, LT in the Unit box. No entry is required in the Unit box for solid dosage forms.

Date: *24 JANUARY 1993*

G	1					/											

11. Arrangements for storage and address(es) of storage premises:

BULK TABLETS WILL BE STORED BRIEFLY AT THE SITE OF MANUFACTURE AND THE SITE OF ASSEMBLY. FINISHED PRODUCT WILL BE STORED BRIEFLY AT THE SITE OF ASSEMBLY, AND FOR DISTRIBUTION AT MSD, CRAMLINGTON, UK.

12. Special precautions for storage:

STORE BELOW 30°C; PROTECT FROM MOISTURE.

13.

Nature of container and closure	Shelf-life (A)	Shelf-life (B)	Pack Size
BLISTER PACKS WITH PVC BASE AND ALUMINIUM FOIL LIDDING.	*24M*		*2*
			6
			10
			12
			18
			20

Unit

Notes: 1) Shelf-life should be expressed in months (M), weeks (W) or days (D) as appropriate eg 3 6 M
A = Unopened.
B = After reconstitution or when the container is opened for the first time, if appropriate.

2) The pack size should contain numbers only, right aligned. If a decimal point is required it should occupy one box.

3) Where applicable enter the unit of measure as MG, GM, ML, LT in the Unit box. No entry is required in the Unit box for solid dosage forms.

Date: *24 JANUARY 1993*

L 1 / [redacted]

16. Name(s) of manufacturers and site(s) of manufacture of (a) the active substance(s) and (b) the dosage form

(a) The active substance(s)

YAMANOUCHI IRELAND CO LTD
DAMASTOWN, MULHADDART
DUBLIN 15
IRELAND [redacted]

OR

(CONTINGENT SOURCE)
YAMANOUCHI PHARMACEUTICAL CO LTD
NO. 1-8, AZUSAWAL-CHOME
ITABASHI-KU, TOKYO, 174, JAPAN

[redacted]

(b) The dosage form

WOELM PHARMA GMBH
MAX-WOELM-STRASSE, 3440 ESCHWEGE
GERMANY [redacted]

OR

MERCK MANUFACTURING DIVISION
MERCK SHARP & DOHME LIMITED
SHOTTON LANE, CRAMLINGTON
NORTHUMBERLAND, NE23 9JU [redacted]

OR [redacted]

MERCK MANUFACTURING DIVISION
MERCK SHARP & DOHME (ITALIA) SPA
VIA EMILIA 21, 27100 PAVIA
ITALY

17. Assembler(s):

BLISTER PACKS

AS THE MANUFACTURERS OF THE DOSAGE FORM

BOTTLE PACKS

MERCK MANUFACTURING DIVISION [redacted]
MERCK SHARP & DOHME BV
WAARDERWEG 39, HAARLEM, NETHERLANDS

18. Importer:

MERCK MANUFACTURING DIVISION
MERCK SHARP & DOHME LIMITED
SHOTTON LANE
CRAMLINGTON
NORTHUMBERLAND
NE23 9JU [redacted]

19. Site and arrangements for quality control:

FULL QUALITY CONTROL TESTING WILL BE PERFORMED AT THE SITE OF MANUFACTURE. IMPORTED MATERIAL WILL BE ACCOMPANIED BY ANALYTICAL PROTOCOLS; IDENTITY TESTING WILL BE CARRIED OUT ON IMPORTED MATERIAL AT MSD, CRAMLINGTON.

20. Distributor (where applicable)

MERCK SHARP & DOHME LIMITED, CRAMLINGTON.

21. List other countries of registration:

FAMOTIDINE TABLETS, 20 AND 40 MG ARE REGISTERED IN MOST COUNTRIES WORLDWIDE FOR PRESCRIPTION USE. APPLICATION FOR OVER-THE-COUNTER USE OF THE 10 MG STRENGTH TABLET WILL BE MADE IN A NUMBER OF COUNTRIES E.G. AUSTRIA, BELGIUM, DENMARK, FRANCE, SWITZERLAND, SWEDEN, USA ETC.

Date: *24 JANUARY 1993*

K 1 / /

14. Pharmacological particulars:

'BLOCAZIDE' IS A POTENT COMPETITIVE H_2-RECEPTOR ANTAGONIST.

'BLOCAZIDE' HAS A RAPID ONSET OF ACTION FOLLOWING ORAL ADMINISTRATION AND, AT THE RECOMMENDED DOSES, 'BLOCAZIDE' HAS A LONG DURATION OF ACTION AND IS HIGHLY EFFECTIVE AT RELATIVELY LOW BLOOD CONCENTRATIONS. DURATION OF ACTION, PLASMA CONCENTRATION, AND URINARY RECOVERY ARE DOSE-RELATED.

'BLOCAZIDE' REDUCES THE ACID AND PEPSIN CONTENT, AS WELL AS THE VOLUME, OF BASAL, NOCTURNAL, AND STIMULATED GASTRIC SECRETION.

IN CLINICAL TRIALS 'BLOCAZIDE' PROVIDED RAPID SYMPTOM RELIEF. WHEN ADMINISTERED BEFORE A TEST MEAL, FAMOTIDINE REDUCED SYMPTOMS THAT WOULD OTHERWISE HAVE BEEN EXPECTED.

AFTER ORAL ADMINISTRATION, A DOSE-RESPONSE RELATIONSHIP WAS CLEARLY DEMONSTRATED FROM 0.5 AND 10 MG FAMOTIDINE IN TERMS OF RAISING GASTRIC PH BETWEEN AND AFTER MEALS. FAMOTIDINE DOSES OF 2.5 TO 10 MG WERE DEMONSTRATED TO PRODUCE A STATISTICALLY SIGNIFICANT EFFECT OF GASTRIC PH AS COMPARED TO PLACEBO. THE ONSET OF EFFECT FOR THE 5 AND 10 MG DOSES WERE SEEN AT APPROXIMATELY 1.5 HOURS POSTDOSE WHILE THAT OF THE 2.5 MG DOSE WAS NOT SEEN UNTIL 2.5 HOURS POSTDOSE. THE MAXIMUM EFFECT, AS MEASURED BY PEAK MEAN PH VALUE, OCCURRED AT 3.5 HOURS. THE ACTIVITY OF THE 5 AND 10 MG DOSES CONTINUED UNTIL APPROXIMATELY 9 HOURS POSTDOSE. FAMOTIDINE IS WELL-TOLERATED AT THESE DOSE LEVELS.

SYSTEMIC EFFECTS OF 'BLOCAZIDE' IN THE CNS, CARDIOVASCULAR, RESPIRATORY OR ENDOCRINE SYSTEMS WERE NOT NOTED IN CLINICAL PHARMACOLOGY STUDIES. ALSO, NO ANTI-ANDROGENIC EFFECTS WERE NOTED IN CLINICAL PHARMACOLOGY STUDIES. SERUM HORMONE LEVELS, INCLUDING PROLACTIN, CORTISOL, THYROXINE (T_4), AND TESTOSTERONE, WERE NOT ALTERED AFTER TREATMENT WITH 'BLOCAZIDE'.

15. Pharmacokinetic particulars:

'BLOCAZIDE' OBEYS LINEAR KINETICS.

IN PHARMACOKINETIC STUDIES IN THE ELDERLY, NO CLINICALLY SIGNIFICANT AGE-RELATED CHANGES WERE DETECTED.

COMPARED TO HISTORICAL DATA FROM YOUNGER SUBJECTS, AGE DOES NOT APPEAR TO AFFECT THE BIOAVAILABILITY OF SINGLE DOSES OF FAMOTIDINE; HOWEVER, THE ELIMINATION APPEARS TO BE REDUCED IN ELDERLY SUBJECTS COMPARED WITH YOUNGER SUBJECTS.

'BLOCAZIDE' IS RAPIDLY ABSORBED WITH DOSE-RELATED PEAK PLASMA CONCENTRATIONS OCCURRING AT 1-3 HOURS. THE MEAN BIOAVAILABILITY OF AN ORAL DOSE IS 40-45%. BIOAVAILABILITY IS NOT CLINICALLY AFFECTED BY THE PRESENCE OF FOOD IN THE STOMACH. 'BLOCAZIDE' UNDERGOES MINIMAL FIRST-PASS METABOLISM. REPEATED DOSES DO NOT LEAD TO ACCUMULATION OF THE DRUG.

PROTEIN BINDING IN THE PLASMA IS RELATIVELY LOW (15-20%). THE PLASMA HALF-LIFE AFTER A SINGLE ORAL DOSE OR MULTIPLE REPEATED DOSES (FOR 5 DAYS) WAS APPROXIMATELY 3 HOURS.

METABOLISM OF THE DRUG OCCURS IN THE LIVER, WITH FORMATION OF THE INACTIVE SULPHOXIDE METABOLITE.

FOLLOWING ORAL ADMINISTRATION, THE MEAN URINARY EXCRETION OF THE ABSORBED DOSE OF FAMOTIDINE IS 65-70%. OF THE TOTAL ORAL DOSE ADMINISTERED, 25-30% IS RECOVERED AS UNCHANGED COMPOUND IN THE URINE. RENAL CLEARANCE IS 250-450 ML/MIN, INDICATING SOME TUBULAR EXCRETION. A SMALL AMOUNT MAY BE EXCRETED AS THE SULPHOXIDE.

A 10 MG CHEWABLE TABLET 'BLOCAZIDE' WAS FOUND TO BE BIOEQUIVALENT TO A 10 MG FILM-COATED TABLET 'BLOCAZIDE'.

Date: *24 JANUARY 1993*

L	1						/										

16. Name(s) of manufacturers and site(s) of manufacture of (a) the active substance(s) and (b) the dosage form

(a) The active substance(s)

YAMANOUCHI IRELAND CO LTD
DAMASTOWN, MULHADDART
DUBLIN 15
IRELAND [redacted]

OR

(CONTINGENT SOURCE)
YAMANOUCHI PHARMACEUTICAL CO LTD
NO. 1-8, AZUSAWAL-CHOME
ITABASHI-KU, TOKYO, 174, JAPAN

[redacted]

(b) The dosage form

WOELM PHARMA GMBH
MAX-WOELM-STRASSE, 3440 ESCHWEGE
GERMANY [redacted]

OR

MERCK MANUFACTURING DIVISION
MERCK SHARP & DOHME LIMITED
SHOTTON LANE, CRAMLINGTON
NORTHUMBERLAND, NE23 9JU [redacted]

OR [redacted]

MERCK MANUFACTURING DIVISION
MERCK SHARP & DOHME (ITALIA) SPA
VIA EMILIA 21, 27100 PAVIA
ITALY

17. Assembler(s):

BLISTER PACKS

AS THE MANUFACTURERS OF THE DOSAGE FORM

BOTTLE PACKS

MERCK MANUFACTURING DIVISION [redacted]
MERCK SHARP & DOHME BV
WAARDERWEG 39, HAARLEM, NETHERLANDS

18. Importer:

MERCK MANUFACTURING DIVISION
MERCK SHARP & DOHME LIMITED
SHOTTON LANE
CRAMLINGTON
NORTHUMBERLAND
NE23 9JU [redacted]

19. Site and arrangements for quality control:

FULL QUALITY CONTROL TESTING WILL BE PERFORMED AT THE SITE OF MANUFACTURE. IMPORTED MATERIAL WILL BE ACCOMPANIED BY ANALYTICAL PROTOCOLS; IDENTITY TESTING WILL BE CARRIED OUT ON IMPORTED MATERIAL AT MSD, CRAMLINGTON.

20. Distributor (where applicable)

MERCK SHARP & DOHME LIMITED, CRAMLINGTON.

21. List other countries of registration:

FAMOTIDINE TABLETS, 20 AND 40 MG ARE REGISTERED IN MOST COUNTRIES WORLDWIDE FOR PRESCRIPTION USE. APPLICATION FOR OVER-THE-COUNTER USE OF THE 10 MG STRENGTH TABLET WILL BE MADE IN A NUMBER OF COUNTRIES E.G. AUSTRIA, BELGIUM, DENMARK, FRANCE, SWITZERLAND, SWEDEN, USA ETC.

Date: *24 JANUARY 1993*