

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-712

MEDICAL REVIEW(S)

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research**

DATE: 9/20/04

FROM: Joyce A Korvick, MD, MPH
DGCDP/ODE III

SUBJECT: Acting Director Summary Approval Comments
NDA 21-712

APPLICANT: Schwartz Pharma, Inc.

DRUG: Fluxid™ (famotidine orally disintegrating tablets)
--20 mg and 40 mg tablets

DIVISION RECOMMENDATION:

The Division has reviewed this submission and recommends that the New Drug Application regarding Fluxid™ (orally disintegrating tablets) be approved for the following indications in adults:

1. *Short term treatment of active duodenal ulcer.* Most adult patients heal within 4 weeks; there is rarely reason to use famotidine at full dosage for longer than 6 to 8 weeks. Studies have not assessed the safety of famotidine in uncomplicated active duodenal ulcer for periods of more than eight weeks.
2. *Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer.* Controlled studies in adults have not extended beyond one year.
3. *Short term treatment of active benign gastric ulcer.* Most adult patients heal within 6 weeks. Studies have not assessed the safety or efficacy of famotidine in uncomplicated active benign gastric ulcer for periods of more than 8 weeks.
4. *Short term treatment of gastroesophageal reflux disease (GERD).* FLUXID™ is indicated for short term treatment of patients with symptoms of GERD (see CLINICAL PHARMACOLOGY IN ADULTS, *Clinical Studies*).

FLUXID™ is also indicated for the short term treatment of esophagitis due to GERD including erosive or ulcerative disease diagnosed by endoscopy (see CLINICAL PHARMACOLOGY IN ADULTS, *Clinical Studies*).

5. *Treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas) (see CLINICAL PHARMACOLOGY IN ADULTS, Clinical Studies).*

Pediatric Indications:

1. *Pediatric use of this formulation is recommended for the treatment of GERD.*

Pediatric use of this formulation is appropriate in younger pediatric patients but its use is limited by the dose of the orally disintegrating tablet (20 or 40 mg) and the recommended daily dosing schedule. Both the age and the weight of the pediatric patient must be taken into consideration when dosing these patients. This tablet is very friable and not scored. Our pediatric use recommendations only include the GERD syndrome and not the other adult indications due to consideration of dosing and lack of available appropriate pediatric formulation of this product to achieve that dosing regimen.

I. Regulatory History:

The following is excerpted from the Medical Officer Summary:

“Pepcid® (famotidine) is an H₂-receptor antagonist which has been approved in the United States since October, 1986 for the treatment of duodenal and gastric ulcer, gastroesophageal Reflux Disease (GERD), and pathological hypersecretory conditions. It is also indicated in children for the treatment of peptic ulcer and GERD. This drug binds to the parietal cell H₂-receptor and competitively inhibits histamine-stimulated gastric acid secretion, thereby raising intragastric pH. It is currently available by prescription as 20-mg and 40-mg tablets, oral suspension (40 mg/5 mL); and parenteral formulations. It is also available as a 10-mg and 20-mg OTC product for the relief and prevention of heartburn and sour stomach.”

“In this submission, the sponsor seeks approval of a new famotidine formulation, an orally disintegrating tablet (ODT), Fluxid® 20-and 40-mg under a 505(b)(2) application. The sponsor relies on the Agency’s finding of safety and efficacy for conventional immediate release famotidine tablets, Pepcid® tablet, originally approved in 1986. Pepcid® is available as injection, tablets, oral suspension and previously as orally disintegrating tablets. The latter was approved on May 28, 1998 (under NDA 20-752) but the company voluntarily ceased its marketing in the U.S., no reason was provided; however, no safety issues were identified. The sponsor has no proposed changes to the indications and administration schedule of the Pepcid®.”

“To support approval, the sponsor conducted a fasting bioequivalence study comparing the 40-mg tablets of the approved Pepcid® and proposed famotidine 40mg orally disintegrating tablets (ODT) dosage forms, Fluxid®. The sponsor requested a waiver of in vivo bioequivalence studies on the 20 mg strength of the drug product. Dr. Tien-Mien Chen from biopharm recommended that biowaiver for the 20 mg ODT can be granted since both 20 and 40 mg strengths of Fluxid

ODT are compositionally proportional and show similar dissolution characteristics. (See Biopharm Review dated 7-13-04). In this trial conducted by the sponsor, a total of 30 healthy subjects were enrolled in a single-dose, randomized, open-label, 3-treatment crossover design study conducted in the United States.”

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OPDRA/DDMAC/DMETS:

DMETS agrees with the proposed Tradename of Fluxid. The DDMAC review recommends against using _____ These have been considered in the labeling negotiations.

B. Chemistry and Manufacturing:

The Chemistry reviewer recommended approval of this formulation. The reviewer stated that two issues needed to be resolved successfully prior to approval: 1.) “the status of impurities eluting at _____ the Determination of Related Substances by HPLC”; 2.) “the analytic procedure and acceptance criterion for Disintegration Time”.

According to the chemistry review regarding the second of the two issues was resolved as follows. In CMC Review #1 (pg. 35 - 36) it was recommended that the analytical procedure be changed to the one described in USP General Chapter <701>, and the acceptance criterion should be established based on the results of tests using this procedure _____ seconds). The current analytical procedure is an in-house method that deviates from <701>.

The applicant agreed to adopt <701> for the test for Disintegration Time, but counter-proposed an acceptance criterion of _____ seconds. A review of data generated by testing several lots of stability samples of Drug Product (stored for _____ at 25 o C/60% RH) using <701>, and a review of the stability data for _____ supports the applicant's counter-proposal. See no. 2 under Responses to Comments in DR Letter Dated August 9, 2004 below. Also see discussion under no. 21, Drug Product section, Responses to Comments in IR Letter Dated July 26, 2004. It appears that, from this point forward, the applicant will use <701> as the Regulatory Analytical Procedure in the Drug Product Specification for release and stability, with an acceptance criterion in both cases of _____ seconds.”

These issues were satisfactorily resolved.

C. Pre-Clinical Pharmacology/Toxicology:

There were no new data submitted in this section. The reviewer recommended updating of this section of the label to conform to current labeling standards. (See pharm/tox labeling review)

D. Biopharmaceutics:

The biopharmaceutics review found Fluxid 40 mg ODT to be bioequivalent to Pepcid 40 mg. A biowaiver was granted for the 20 mg dose.

E. Clinical/Statistical:

Efficacy:

There are no new efficacy trials submitted with this NDA. To support approval, the sponsor conducted bioequivalence study (SP701) comparing the 40-mg tablets of the approved Pepcid® and proposed Fluxid® orally disintegrating tablet dosage forms, and relies on the Agency's finding of safety and efficacy for Pepcid®. The results of Study SP701 have shown that Fluxid 40mg ODT, when taken with or without water is bioequivalent to the reference product (Pepcid® 40mg) under fasting conditions.

Bioequivalence of famotidine with respect to the log-transformed (ln) AUC(0-t), AUC(0-inf), and Cmax were all within the acceptable range of 80% to 125%. When administered with water: ln (Cmax), at 3.61% to 109.85%, ln [AUC(0-t)], at 98.05% to 111.94%, and ln [AUC(0-int)], at 98.08% to 111.55%. When administered without water: ln (Cmax), at 94.73% to 111.16%, ln [AUC(0-t)], at 97.10% to 110.86%, and ln [AUC(0-int)], at 97.09% to 110.42%. The Biopharmaceutics reviewers found this acceptable data in support of the bioequivalence of Fluxid® to Pepcid®.

Safety:

Given that Fluxid is bioequivalent to Pepcid there are no additional safety issues raised in this application. The medical reviewer's comments are as follows:

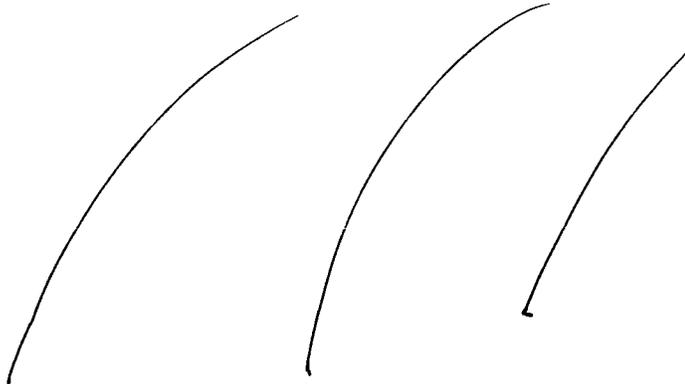
"The risk associated with famotidine ODT are not expected to be different from those associated with marketed Pepcid tablets. The combination of postmarketing data, previous clinical trials and adverse events analysis with study SP701 establish the safety of Fluxid®. Single dose of Fluxid® was well tolerated in the study. This study shows that famotidine 40mg ODT has a similar safety profile when compared to the referenced listed drug, Pepcid 40mg tablets. For famotidine ODT, the most common treatment related AE was nausea (3.3%). In controlled clinical trials with Pepcid tablets, the adverse reactions reported in more than 1% of patients on therapy that maybe causally related to the drug were headache (4.7%), dizziness (1.3%), diarrhea (1.7%), and constipation (1.2%)."

Pediatric Use:

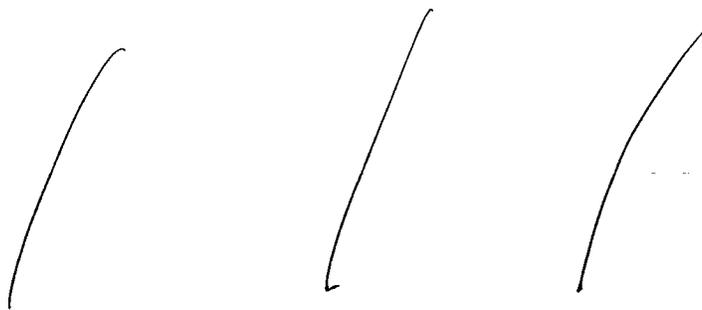
The current label for Pepcid includes the following indications and dosing recommendations for pediatric patients:

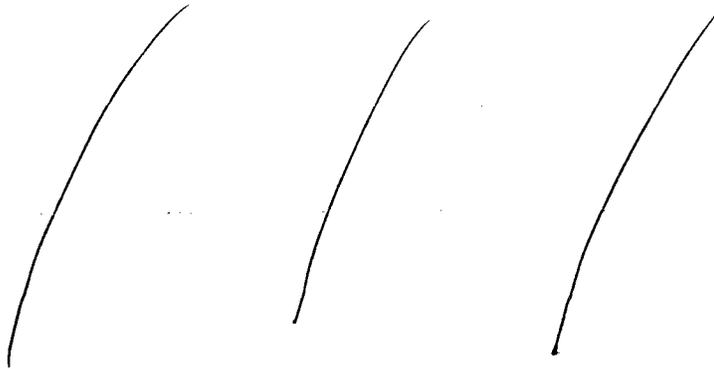
- GERD in <1 year old
infants < 3 months: 0.5 mg/kg/dose once daily (up to 8 weeks)
infants 3 months to < 1 year: 0.5 mg/kg/dose twice daily (up to 8 weeks)
- GERD (with or without esophagitis including erosions and ulcerations)
1-16 years old
1.0 mg/kg/day p.o. divided b.i.d. up to 40 mg b.i.d.
- Peptic Ulcer in 1-16 years old
0.5 mg/kg/day p.o. at bedtime or divided b.i.d. up to 40 mg/day.
package insert.

The approved Pepcid® products have a common package insert for the suspension, tablets, and injectable formulations; the dosing for pediatric patients is calculated on a mg/kg basis. The sponsor's proposal



III. Labeling Recommendations:





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IV. Phase IV Commitments:

No phase IV Commitments or Risk Management Plans are required based upon review of this submission.

V. Pediatric Waiver Request:

On 7/26/04 a full Pediatric Waiver was granted by the Division to Schwartz Pharma. The following is from that letter:

“We have reviewed the submission and agree that a waiver is justified for Famotidine Orally Disintegrating Tablets, 20 mg and 40 mg for treatment of GERD with or without esophagitis and peptic ulcer in pediatric patients because there are other age appropriate formulations (such as suspension) for famotidine products available on the market that adequately address pediatric dosing information.”

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

/s/

Joyce Korvick
9/24/04 04:53:53 PM
MEDICAL OFFICER

CLINICAL REVIEW

Clinical Review NDA 21-712

**APPEARS THIS WAY
ON ORIGINAL**

CLINICAL REVIEW

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA: 21-712

Type of Submission: 505(b)(2)

Sponsor: Schwarz Pharma, Inc.
6140 West Executive Drive
Mequon, WI 53092-4467

Date Submitted: November 25, 2003

Drug Name: Famotidine Orally Disintegrating Tablet
20- and 40-mg

Drug Class: H2-Receptor Antagonist

Proposed Indication: Duodenal ulcer
Benign Gastric Ulcer
Gastroesophageal Reflux Disease (GERD)
Pathological Hypersecretory Conditions

Documents Reviewed: Clinical Section of the NDA

Division Director: Robert Justice, M.D., M.S.

Deputy Director: Joyce Korvick, M.D., M.P.H.

Team Leader: Ruyi He, M.D.

Medical Officer: Lolita A. Lopez, M.D.

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Clinical Review for NDA 21-712

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Famotidine Orally Disintegrating Tablet is recommended to be approvable by this medical officer for the following indications:

- Short term treatment of active duodenal ulcer
- Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer.
- Short term treatment of benign gastric ulcer
- Short term treatment of gastroesophageal reflux disease (GERD)
- Pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas)

To obtain approval, the sponsor should incorporate the labeling recommendations of listed in the Medical Officer's Labeling Review (see Appendix A).

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

There is no recommendation for Phase IV commitments or Risk management based on my review.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Pepcid® (famotidine) is an H₂-receptor antagonist which has been approved in the United States since October, 1986 for the treatment of duodenal and gastric ulcer, gastroesophageal Reflux Disease (GERD), and pathological hypersecretory conditions. It is also indicated in children for the treatment of peptic ulcer and GERD. This drug binds to the parietal cell H₂-receptor and competitively inhibits histamine-stimulated gastric acid secretion, thereby raising intragastric pH. It is currently available by prescription as 20-mg and 40-mg tablets, oral suspension (40 mg/5 mL); and parenteral formulations. It is also available as a 10-mg and 20-mg OTC product for the relief and prevention of heartburn and sour stomach.

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In this submission, the sponsor seeks approval of a new famotidine formulation, an orally disintegrating tablet (ODT), Fluxid® 20-and 40-mg under a 505(b)(2) application. The sponsor relies on the Agency's finding of safety and efficacy for conventional immediate release famotidine tablets, Pepcid® tablet, originally approved in 1986. Pepcid® is available as injection, tablets, oral suspension and previously as orally disintegrating tablets. The latter was approved on May 28, 1998 (under NDA 20-752) but the company voluntarily ceased its marketing in the U.S., no reason was provided; however, no safety issues were identified. The sponsor has no proposed changes to the indications and administration schedule of the Pepcid®.

To support approval, the sponsor conducted a fasting bioequivalence study comparing the 40-mg tablets of the approved Pepcid® and proposed famotidine 40mg orally disintegrating tablets (ODT) dosage forms, Fluxid®. The sponsor requested a waiver of in vivo bioequivalence studies on the 20 mg strength of the drug product. Dr. Tien-Mien Chen from biopharm recommended that biowaiver for the 20 mg ODT can be granted since both 20 and 40 mg strengths of Fluxid ODT are compositionally proportional and show similar dissolution characteristics. (See Biopharm Review dated 7-13-04). In this trial conducted by the sponsor, a total of 30 healthy subjects were enrolled in a single-dose, randomized, open-label, 3-treatment crossover design study conducted in the United States.

B. Efficacy

There are no new efficacy trials submitted with this NDA. To support approval, the sponsor conducted bioequivalence study (SP701) comparing the 40-mg tablets of the approved Pepcid® and proposed Fluxid® orally disintegrating tablet dosage forms, and relies on the Agency's finding of safety and efficacy for Pepcid®. The results of Study SP701 have shown that Fluxid 40mg ODT, when taken with or without water is bioequivalent to the reference product (Pepcid® 40mg) under fasting conditions. Bioequivalence of famotidine with respect to the log-transformed (*ln*) AUC(0-t), AUC(0-inf), and C_{max} were all within the acceptable range of 80% to 125%. When administered with water: *ln* (C_{max}), at 93.61% to 109.85%, *ln* [AUC(0-t)], at 98.05% to 111.94%, and *ln* [AUC(0-int)], at 98.08% to 111.55%. When administered without water: *ln* (C_{max}), at 94.73% to 111.16%, *ln* [AUC(0-t)], at 97.10% to 110.86%, and *ln* [AUC(0-int)], at 97.09% to 110.42%.

The efficacy of famotidine is related to its ability to reduce basal and nocturnal gastric acid secretions. It competitively inhibits the binding of histamine to H₂-receptors on the gastric basolateral membrane of parietal cells, reducing basal and nocturnal gastric acid secretions. The drug also decreases the gastric acid response to stimuli such as food, caffeine, insulin, betazole, or pentagastrin. Famotidine reduces the total volume of gastric juice, thus indirectly decreasing pepsin

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secretion. The drug does not appear to alter gastric motility, gastric emptying, esophageal pressures, biliary secretions, or pancreatic secretions. Famotidine may aid in gastromucosal healing, and it may protect the mucosa from the irritant effects caused by aspirin and nonsteroidal anti-inflammatory agents.

C. Safety

Famotidine has been proven safe and effective in the U.S. for almost 18 years; a 20 mg tablet is available for OTC use.

The risk associated with famotidine ODT are not expected to be different from those associated with marketed Pepcid tablets. The combination of postmarketing data, previous clinical trials and adverse events analysis with study SP701 establish the safety of Fluxid®. Single dose of Fluxid® was well tolerated in the study. This study shows that famotidine 40mg ODT has a similar safety profile when compared to the referenced listed drug, Pepcid 40mg tablets. For famotidine ODT, the most common treatment related AE was nausea (3.3%). In controlled clinical trials with Pepcid tablets, the adverse reactions reported in more than 1% of patients on therapy that maybe causally related to the drug were headache (4.7%), dizziness (1.3%), diarrhea (1.7%), and constipation (1.2%).

D. Dosing

The sponsor is proposing the following:

Dose:

Famotidine orally disintegrating tablet (ODT), 20- and 40-mg (Fluxid®)

Indications:

Adults

- Duodenal ulcer
Acute Therapy (4-8 weeks): 40 mg once a day at bedtime or 20 mg b.i.d
Maintenance Therapy: 20 mg once a day at bedtime
- Benign Gastric Ulcer
Acute Therapy: 40 mg once a day at bedtime.
- Gastroesophageal Reflux Disease (GERD)
Treatment of symptoms of GERD: 20 mg b.i.d. for up to 6 weeks
Treatment of GERD with esophagitis including erosions and ulcerations: 20 or 40 mg b.i.d. for up to 12 weeks
- Pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas)
Treatment: 20 to 160 mg every 6 hours

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Pediatrics

- GERD (with or without esophagitis including erosions and ulcerations)
— years old
1.0 mg/kg/day p.o. divided b.i.d. up to 40 mg b.i.d.

The approved Pepcid® products have a common package insert for the suspension, tablets, and injectable formulations; the dosing for pediatric patients is calculated on a mg/kg basis. The sponsor's proposal

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

The treatment for overdosage is symptomatic and supportive, unabsorbed material should be removed from the gastrointestinal tract. Oral dosages of up to 640 mg/day have been given to adult patients with pathological hypersecretory conditions with no serious adverse effects. This is addressed in the prescription package insert.

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E. Special Populations

Since this NDA only contains bioequivalent studies conducted in healthy patients, there are no new data regarding the effects of gender, race or age on safety or efficacy. The sponsor refers to the information in the current label for Pepcid®.

Pediatric

Pediatric patients were not evaluated in this NDA. No data were submitted by the sponsor regarding this population. Famotidine is indicated for the treatment of peptic ulcer and GERD with or without esophagitis including erosions and ulcerations.

Geriatric

No new data for this new famotidine orally disintegrating tablet formulation were submitted by the sponsor regarding this population. The package insert for Pepcid® states that no dosage adjustment is required based on age. Famotidine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Dosage adjustment in the case of moderate or severe renal impairment is necessary.

Patients with Moderate or Severe Renal Insufficiency

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

Pregnancy Use

This application has no new information regarding pregnant women. Famotidine is currently listed as Pregnancy Category B. There are no adequate or well-controlled studies in pregnant women; therefore, this drug should be used during pregnancy only if clearly needed.

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Nursing Mothers

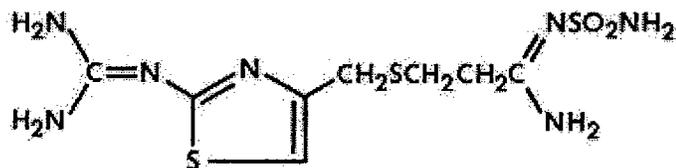
Famotidine is detectable in human milk. Because of the potential for serious adverse reactions in nursing infants from this drug, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Drug: Famotidine orally disintegrating tablet (Fluxid®), 20 and 40 mg



Drug Class: H₂-receptor antagonist

Proposed Indications:

Adults

- Duodenal ulcer
- Benign Gastric Ulcer
- Gastroesophageal Reflux Disease (GERD)
- Pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas)

Pediatrics

- GERD with or without esophagitis

Regimen:

Adults

Duodenal ulcer

Acute Therapy (4-8 weeks): 40 mg once a day at bedtime or 20 mg b.i.d

Maintenance Therapy: 20 mg once a day at bedtime

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Benign Gastric Ulcer

Acute Therapy: 40 mg once a day at bedtime.

Gastroesophageal Reflux Disease (GERD)

Treatment of GERD symptoms: 20 mg b.i.d. for up to 6 weeks

Treatment of GERD with esophagitis including erosions and ulcerations:
20 or 40 mg b.i.d. for up to 12 weeks

Pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome,
multiple endocrine adenomas)

Treatment: 20 to 160 mg every 6 hours

Pediatrics

GERD (with or without esophagitis including erosions and ulcerations)

— years old

1 mg/kg/day p.o. divided b.i.d. up to 40 mg b.i.d.

B. State of Armamentarium for Indication(s)

There are four H₂-receptor antagonists (famotidine, cimetidine, ranitidine and nizatidine) approved for use in the United States. Currently, famotidine, cimetidine, and ranitidine are being used for heartburn and acid-related gastrointestinal disorders and are all available for OTC use. The applicant is seeking the approval of famotidine orally disintegrating tablet, 20 and 40-mg for prescription use.

C. Important Milestones in Product Development

Pepcid® was approved by the FDA in October, 1986 for the treatment of a variety of acid-related gastrointestinal disorders including active duodenal and acute benign gastric ulcer. It is also approved for the treatment of pathological hypersecretory conditions, e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas. On December 10, 1991, it was approved for the treatment of gastritis, acute symptomatic and erosive gastroesophageal reflux disease (GERD). Pepcid AC 10mg and 20mg became available on for OTC use April 30, 1995 and September 23, 2003 respectively for the relief and prevention of heartburn, acid indigestion and sour stomach.

Pepcid® is currently available by prescription as 20-mg and 40-mg tablets, oral suspension (40 mg/5 mL), and parenteral formulations. An orally disintegrating tablet was approved on May 28, 1998 (under NDA 20-752) but the company

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voluntarily ceased its marketing in the U.S., no reason was provided; however, no safety issues were identified. On January 3, 2003 and April 2, 2003, the Agency sent the sponsor, Schwarz Pharma, Inc. a correspondence discussing the clinical development of famotidine orally disintegrating tablet (ODT) as an alternative to Pepcid® (famotidine) tablets. On November 25, 2003, the sponsor submitted NDA 21-712 seeking the approval of famotidine ODT 20 and 40mg for prescription use under a 505(b)(2) application using Merck's Pepcid® product as its reference listed drug.

D. Other Relevant Information

Famotidine is marketed in 68 countries worldwide. The marketing approval or application of famotidine has not known to have been rejected, suspended, revoked, or withdrawn by an Agency in any country.

E. Important Issues with Pharmacologically Related Agents

Among the H₂-receptor blockers, it is known that cimetidine is more likely than others to provoke interactions with hepatically metabolized drugs. Famotidine is less likely than cimetidine to interact with other drugs.

Some clinicians believe that this drug class cause adverse CNS effects but retrospective literature could not identify one H₂-receptor antagonist as being more likely than the others to cause this reaction. CNS reactions are more likely to occur in elderly patients and/or those with renal impairment.

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

In this 505(b)(2) application, the sponsor submitted bioequivalence studies to bridge famotidine orally disintegrating tablets to Pepcid® tablets and to FDA's previous finding of safety and effectiveness for Pepcid®. Bioequivalence of famotidine with respect to the ln-transformed AUC(0-t), AUC(0-inf), and C_{max} was concluded if the 90% confidence interval of the ratio of the product means for each parameter fell within the range of 80% to 125%.

Tien-Mien Chen, Ph.D. from Clinical Pharmacology and Biopharmaceutics conducted the biopharmaceutics review.

No new animal or toxicology studies were submitted and microbiology studies are not applicable for this drug class. In the current present package insert report, animal studies showed no evidence of carcinogenic potential for famotidine. In rat studies, fertility and reproductive performance were not affected and there were no direct fetotoxic effects

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observed. However, sporadic abortions occurred at oral doses of 250 times the usual human dose or higher in some rabbits displaying marked decrease in food intake.

III. Human Pharmacokinetics and Pharmacodynamics

The sponsor submitted a study to evaluate the single dose bioequivalence of the test product, a 40 mg famotidine ODT formulation administered with and without water, compared with the reference product, Merck's Pepcid® (40 mg famotidine tablet) when administered with water following a single 40 mg dose in the fasted state. The sponsor requested a waiver of in vivo bioequivalence studies on the 20 mg strength of the drug product. Dr. Tien-Mien Chen from biopharm recommended that biowaiver for the 20 mg ODT can be granted since both 20 and 40 mg strengths of Fluxid ODT are compositionally proportional and show similar dissolution characteristics. (See Biopharm Review dated 7-13-04).

A. Pharmacokinetics

This bioequivalence study showed that the famotidine ODT formulation when given with or without water resulted in similar rate and extent of famotidine exposure compared to the reference Pepcid® tablet. Bioequivalence of famotidine with respect to the log-transformed (*ln*) AUC(0-t), AUC(0-inf), and Cmax were all within the acceptable range of 80% to 125%. When administered with water: *ln* (Cmax), at 93.61%-109.85%, *ln* [AUC(0-t)], at 98.05% -111.94%, and *ln* [AUC(0-int)], at 98.08% -111.55%. When administered without water: *ln* (Cmax), at 94.73%-111.16%, *ln* [AUC(0-t)], at 97.10% -110.86%, and *ln* [AUC(0-int)], at 97.09% -110.42%.

Please refer to FDA's Biopharm Review of NDA 21-712. For human pK information, please see the prescription package insert of Pepcid tablets.

B. Pharmacodynamics

There is no new pharmacodynamic data in this submission. Famotidine reduces basal and nocturnal gastric acid secretions by competitively inhibiting the binding of histamine to H₂-receptors on the gastric basolateral membrane of parietal cells. The drug also decreases the gastric acid response to stimuli such as food, caffeine, insulin, betazole, or pentagastrin. Famotidine reduces the total volume of gastric juice, thus indirectly decreasing pepsin secretion. The drug does not appear to alter gastric motility, gastric emptying, esophageal pressures, biliary secretions, or pancreatic secretions. Famotidine may aid in gastromucosal healing, and it may protect the mucosa from the irritant effects caused by aspirin and nonsteroidal anti-inflammatory agents.

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IV. Description of Clinical Data and Sources

A. Overall Data

Clinical section of the NDA (paper copy)
Fluxid Electronic Label
Package Insert of Pepcid®
Pharmacology Online Monograph for Famotidine

B. Tables Listing the Clinical Trials

Table 1: Clinical Trial SP701

Study Name	Design	No. of Patients	Dosage	Location
SP701	Randomized, Single-dose, open-label, 3 treatment, crossover	30 enrolled 28 completed	40 mg Famotidine ODT	//

C. Postmarketing Experience

It is estimated that around $\frac{1}{2}$ patients had used OTC famotidine in the United States and over $\frac{1}{2}$ prescriptions for oral formulations had been dispensed in the United States from 1993 through 2002.

A review of the Adverse Experience Reports for patients treated with oral formulations of famotidine shows that the percentage of adverse experiences are similar for the various dosage formulations.

D. Literature Review

The applicant submitted multiple references/articles from peer reviewed journal, and summary of basis of approval for Pepcid®.

V. Clinical Review Methods

A. How the Review was Conducted

The applicant's proposal for the use of famotidine ODT was based on a bioequivalence study, SP701, comparing famotidine 40 mg ODT and Pepcid® 40mg tablets. A multispecialty review was done by physicians, biopharmaceutics, chemists, and a project manager.

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B. Overview of Materials Consulted in Review

Clinical Section of NDA 21-712, printed material
Fluxid® Electronic Label
Package insert: Pepcid® mg tablets
Physicians' Desk Reference Online
Pharmacology Online
Orange Book
Basic and Clinical Pharmacology-8th Ed., Bertram Katzung, Lange/McGraw Hill
Goodman and Gilman's Pharmacological Basis of Therapeutics, 9th Ed.,
Pergamon Press
Medical Officer's Review of NDA 20-325, S-015
Medical Officer's Review of NDA 19-462
Medical Officer's Review of NDA 20-752

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

A comprehensive review of Study SP701 bioequivalence study was conducted. A DSI audit was conducted for this study and report is still pending at the time of completion of this review.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

All studies submitted in this NDA were conducted in accordance with the Declaration of Helsinki and in accordance with Good Clinical Practice.

E. Evaluation of Financial Disclosure

The applicant submitted an FDA Form 3454 certifying that none of the investigators of the covered clinical studies had any financial interests to disclose.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

There were no efficacy evaluations submitted with this NDA. To support approval, the sponsor conducted bioequivalence study (SP701) comparing the 40-mg tablets of the approved Pepcid® and proposed Fluxid® ODT dosage forms, and relies on the Agency's finding of safety and efficacy for Pepcid®. The study showed that the Fluxid® ODT formulation when given with or without water resulted in similar rate and extent of famotidine exposure compared to the reference Pepcid® tablet. Bioequivalence of famotidine with respect to the log-transformed AUC(0-t), AUC(0-inf), and Cmax were all within the acceptable range of 80% to 125%.

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B. General Approach to Review of the Efficacy of the Drug

Efficacy was assessed by utilizing the data submitted by the applicant, a bioequivalence study comparing famotidine ODT 40mg and Pepcid tablet 40mg. By showing that the two products have equivalent AUCs and C_{max} (famotidine exposure), it is deemed that the trials will provide a bridge from famotidine ODT to Pepcid tablets (20 and 40 mg) and to FDA's previous finding of safety and efficacy for famotidine.

C. Detailed Review of Trials by Indication

A full summary and review of the trial is included in the appendix.

D. Efficacy Conclusions

In summary, a comparison of the pharmacokinetics of famotidine ODT and Pepcid® tablets administered with and without water in healthy subjects was conducted to support the proposed indications.

Using standard definitions of bioequivalence (mean ratios of test to reference and 90% CIs of 80% to 125%), famotidine ODT and Pepcid® tablets (40mg) were bioequivalent with respect to ln-transformed AUC(0-t), AUC(0-inf), and C_{max}. Bioequivalence of famotidine with respect to the log-transformed (ln) AUC(0-t), AUC(0-inf), and C_{max} were all within the acceptable range of 80% to 125%. When administered with water: ln (C_{max}), at 93.61%-109.85%, ln[AUC(0-t)], at 98.05% -111.94%, and ln[AUC(0-int)], at 98.08% -111.55%. When administered without water: ln (C_{max}), at 94.73%-111.16%, ln [AUC(0-t)], at 97.10% - 110.86%, and ln [AUC(0-int)], at 97.09% -110.42%.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Famotidine is an H₂-receptor antagonist which has been proven safe and effective for almost 18 years for the treatment of acid related disorders. It is currently available by prescription as 20-mg and 40-mg tablets, oral suspension (40 mg/5 mL); and parenteral formulations. A 10-mg OTC product has been available for nine years and a 20-mg OTC product has been available for almost a year now. The combination of postmarketing data, previous clinical trials and adverse events analysis with study, SP701, establish the safety of famotidine ODT.

Single doses of famotidine ODT tablet were well tolerated. There were no deaths in this trial and no reported adverse events were severe in intensity, there was no

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withdrawal due to an adverse event. This study (SP701) shows that famotidine 40mg ODT has a similar safety profile when compared to the referenced listed drug, Pepcid 40mg tablets. The following tables show the adverse events for the trial.

Table 2: Adverse Events by Body System

Body System Adverse Event	Famotidine 40 mg ODT (N = 60) n (%) [AEs]		Famotidine 40 mg Tablets (N = 28) n (%) [AEs]
	With water (N = 30)	Without water (N = 30)	
Subjects with at least one AE	5 (16.7) {11}	5 (16.7) {9}	2 (7.1) {2}
<i>Body as a whole, general</i>			
Fever	1 (1.7) {1}	0	0
<i>Central & peripheral nervous</i>			
Headache	0	0	2 (7.1) {2}
Dizziness	1 (1.7) {1}	0	0
<i>Gastrointestinal</i>			
Nausea	2 (3.3) {2}	1 (1.7) {1}	0
Diarrhea	1 (1.7) {1}	0	0
Dyspepsia	1 (1.7) {1}	0	0
Vomiting	1 (1.7) {1}	0	0
<i>Liver & biliary</i>			
SGPT increased	0	1 (1.7) {1}	0
<i>Musculoskeletal</i>			
Back pain	1 (1.7) {1}	0	0
<i>Red blood cell</i>			
Anemia	(1.7) {1}	1 (1.7) {2}	0
<i>Reproductive, female</i>			
Dysmenorrhea	(1.7) {1}	0	0
<i>Resistance mechanism</i>			
Herpes simplex	1 (1.7) {1}	0	0
<i>Urinary</i>			
Urine abnormal	0	2 (3.3) {3}	0
Hematuria	0	1 (1.7) {1}	0
Pyuria	0	1 (1.7) {1}	0

Adapted from sponsor's submission p.295

n = number of subjects with the AE (AEs) = number of AEs reported

A subject may have had more than one AE

The table below is a summary of considered treatment-related adverse events.

Table 3: Treatment Related Adverse Events

Body System Adverse Event	Famotidine 40mg ODT (N=60) n (%)	Famotidine 40mg Tablets (N=60) n (%)
Central & Peripheral Nervous Dizziness	1 (1.7)	0
Gastrointestinal Nausea	2 (3.3)	0
Dyspepsia	1 (1.7)	0
Liver & Biliary SGOT increased	1 (1.7)	0

Adapted from sponsor's submission p. 236

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The most common treatment related adverse event for famotidine ODT was nausea (3.3%, N=2/60). The only adverse event considered possibly related to famotidine ODT that has not been reported with famotidine ODT is dyspepsia. One patient had an elevated SGPT; unspecified liver enzyme abnormalities have been associated with Pepcid® and is described in the package insert. In controlled clinical trials with Pepcid tablets, the adverse reactions reported in more than 1% of patients on therapy that maybe causally related to the drug were headache (4.7%), dizziness (1.3%), diarrhea (1.7%), and constipation (1.2%). See Tables 2 and 3.

B. Description of Patient Exposure

A total of 30 healthy adult subjects were enrolled in this three-treatment randomized, crossover design study comparing famotidine 40mg as orally disintegrating tablet placed on the tongue taken with or without water and Pepcid® tablet taken with water. Each treatment is separated by a one week washout period. Thirty (30) subjects received a Famotidine 40 mg ODT with water and thirty (30) subjects received a Famotidine 40 mg ODT without water. Twenty-eight (28) subjects received a Famotidine 40 mg Tablet (Pepcid®); two (2) subjects withdrew for personal reasons prior to the Famotidine 40 mg Tablet period.

C. Methods and Specific Findings of Safety Review

Study SP701 was reviewed in this submission to assess the bioequivalence of famotidine ODT and Pepcid® (40mg). This trial was not specifically conducted to assess safety issues with this orally disintegrating formulation of famotidine. The subjects in these trials were healthy volunteers.

D. Adequacy of Safety Testing

This is a 505(b)(2) submission. For the trials in this NDA, the sponsor performed the appropriate safety monitoring for the subjects.

E. Summary of Critical Safety Findings and Limitations of Data

Overall, famotidine ODT appears safe to use for the proposed indications in adults and older pediatric patients who are able to follow instructions in taking an orally disintegrating tablet.

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VIII. Dosing, Regimen, and Administration Issues

The sponsor is proposing the following:

Dose:

Famotidine orally disintegrating tablet (ODT), 20- and 40-mg (Fluxid®)

Indications:

Adults

- Duodenal ulcer
Acute Therapy (4-8 weeks): 40 mg once a day at bedtime or 20 mg b.i.d
Maintenance Therapy: 20 mg once a day at bedtime
- Benign Gastric Ulcer
Acute Therapy: 40 mg once a day at bedtime.
- Gastroesophageal Reflux Disease (GERD)
Treatment of symptoms of GERD: 20 mg b.i.d. for up to 6 weeks
Treatment of GERD with esophagitis including erosions and ulcerations: 20 or 40 mg b.i.d. for up to 12 weeks
- Pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas)
Treatment: 20 to 160 mg every 6 hours

Pediatrics

- GERD (with or without esophagitis including erosions and ulcerations)
— years old
1.0 mg/kg/day p.o. divided b.i.d. up to 40 mg b.i.d.

Directions for use: Just prior to administration, remove the tablet from the bottle with dry hands. Immediately place the famotidine ODT on top of the the tongue where it will dissolve in seconds, then swallow with saliva. Administration with liquid is not necessary.

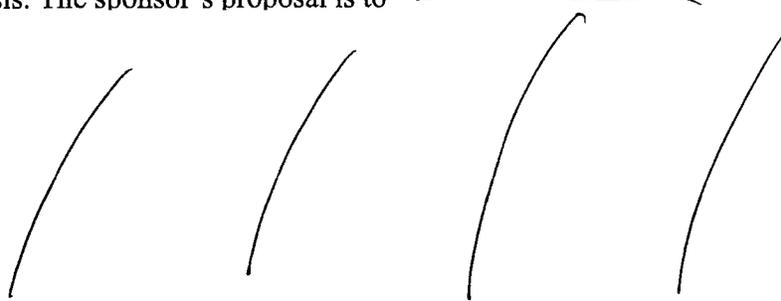
Study SP701 have shown that Fluxid® tablets dissolve between from — to — and the mean disintegration time was 76.63 seconds (almost 1½ mins.) with a SD of 38.77 seconds. See tables 4 and 5 of appendix B. Therefore, the claim that

Patients should be informed of the range of time it may take for this product to dissolve. This should be communicated in the package insert.

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The approved Pepcid® products have a common package insert for the suspension, tablets, and injectable formulations; the dosing for pediatric patients is calculated on a mg/kg basis. The sponsor's proposal is to



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

IX. Use in Special Populations

The trial included in this NDA is a bioequivalence study conducted in healthy patients; therefore, there are no new data regarding the effects of gender, race or age on safety or efficacy. The sponsor refers to the information in the current labeling of Pepcid®.

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

No new data regarding gender effects were submitted with this submission. There are no known differences in efficacy or safety based on gender with the use of famotidine.

In this study, females comprise 40% while males comprise 60% of the population.

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B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

There are no new data concerning the effect of age, race or ethnicity on safety and efficacy with the use of famotidine were submitted with this application. There are no known differences in efficacy or safety based on race or ethnicity with the use of famotidine.

In the Prilosec® package insert, it is stated that no dosage adjustment is required based on age. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

In this study, 76% were Caucasians, 10% were European/Middle Eastern, 10% were Hispanics and 3% (1 male) was Asian. The overall mean age of the subjects was 30 years (range 20-50 years), and the mean weight was 157.6 pounds (range 100-201 pounds).

C. Evaluation of Pediatric Program

No data regarding pediatric population were included in this submission. The applicant requested for a waiver of pediatric studies. The waiver was granted because there are other age appropriate formulation (such as suspension) for famotidine products available on the market that adequately addresses pediatric dosing information. Also see section VIII of this review.

D. Comments on Data Available or Needed in Other Populations

Pepcid® has been used widely in the pediatric and geriatric population. The current prescription label states that no dosage adjustment is required based on age, however, because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

X. Conclusions and Recommendations

A. Conclusions

A comparison of the pharmacokinetics of famotidine orally disintegrating tablet, 40 mg and Pepcid 40 mg tablets in healthy subjects (Study SP701) was conducted to support the following indications: acute therapy of benign gastric ulcer and treatment of pathological hypersecretory conditions

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The sponsor seeks approval of famotidine orally disintegrating tablet (ODT) 20 and 40-mg, Fluxid® or Zyflux® under a 505(b)(2) application and relies on the Agency's finding of safety and efficacy for conventional immediate release famotidine tablets, Merck's Pepcid®. In this proposed new formulation, famotidine can be administered as orally disintegrating tablet formulation.

The study showed that the Fluxid® 40mg ODT formulation when given with or without water resulted in similar rate and extent of famotidine exposure compared to the reference Pepcid® 40mg tablet. Bioequivalence of famotidine with respect to the log-transformed AUC(0-t), AUC(0-inf), and Cmax were all within the acceptable range of 80% to 125%.

This study (SP701) shows that famotidine 40mg ODT has a similar safety profile when compared to the referenced listed drug, Pepcid 40mg tablets. The most common treatment related adverse event for famotidine ODT was nausea (3.3%). The combination of postmarketing data, previous clinical trials and adverse events analysis with study, SP701, establish the safety of famotidine ODT.

This famotidine ODT formulation will benefit patients who prefer not to take water after administering drugs in the tablet form.

B. Recommendations

From a clinical standpoint, the bioequivalence studies submitted by the applicant revealed that Fluxid® appears to be comparable to Pepcid® tablets and therefore, supports the approval of Fluxid ODT. This NDA supports the following indications: acute therapy of benign gastric ulcer and treatment of pathological hypersecretory conditions in

The sponsor should incorporate the labeling changes recommended by the review team.

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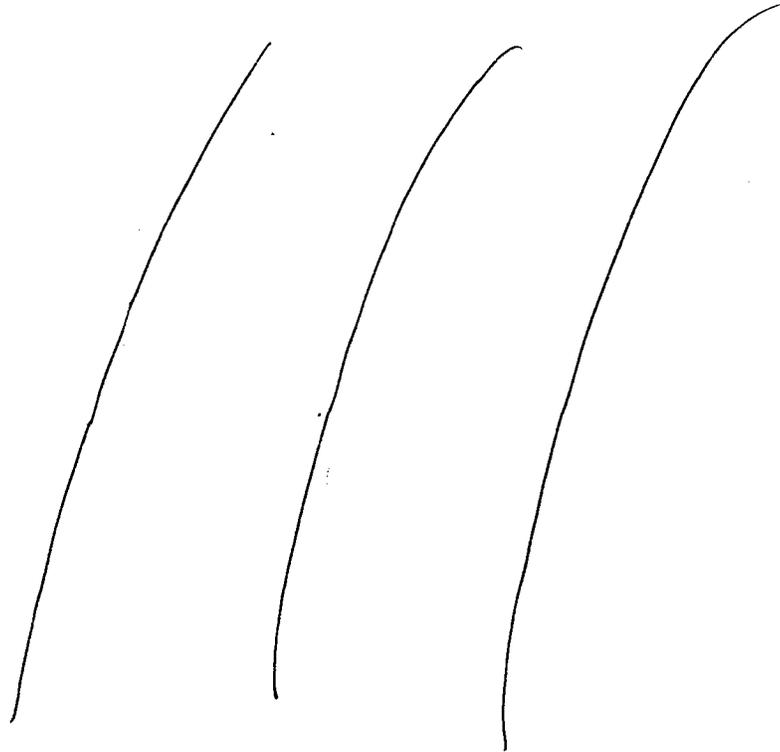
§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

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B. Individual More Detailed Study Reviews

Study SP701

A Pharmacokinetic Study to Evaluate the Bioequivalence of a Unique New Formulation (Test), Orally Disintegrating Tablet (ODT), of Famotidine 40 mg, Administered With and Without Water, Compared to a Marketed Famotidine 40 mg Tablet Formulation (Reference) Pepcid®, by Merck

Clinical Phase I

Study Period: January 25, 2003 to February 10, 2003.

Objective:

To evaluate the single dose bioequivalence of the test product, a 40 mg famotidine ODT formulation administered with and without water,

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compared with the reference product, Pepcid® (40 mg famotidine tablet) (Merck), when administered with water following a single 40 mg dose in the fasted state.

Study Design

This is a single-dose, randomized, open-label, 3-treatment crossover study.

A total of 30 healthy male and/or female subjects were enrolled to ensure that at least 24 complete the study.

The subjects were screened within 21 days prior to study enrollment. The screening procedure included medical history, physical examination (height, weight, frame size, vital signs, and ECG), and clinical laboratory tests (hematology, serum chemistry, urinalysis, HIV antibody screen, hepatitis B surface antigen screen, hepatitis C antibody screen, serum pregnancy [females only]), and a screen for cannabinoids.

Subjects reported to the clinic on the evening prior to each dosing and received a snack at 1900. The subjects then observed a 10-hour overnight fast. On Day 1, a standardized meal schedule was initiated with lunch at 1030, dinner at 1500, and a snack at 1900.

During the study, the subjects were to remain in an upright position (sitting or standing) for 4.5 hours after the famotidine was administered. Water was restricted 1 hour predose until 1 hour postdose. Food was restricted 10 hours predose until 4 hours postdose. Subjects were not allowed to engage in any strenuous activity during the study.

Vital signs, sitting (blood pressure and heart rate), were assessed each morning prior to dosing. A clinical laboratory evaluation (hematology, serum chemistry, and urinalysis), an ECG, and a physical examination including sitting vital signs (blood pressure, pulse, respirations, and temperature) were performed at the completion of the study. Adverse events were monitored.

Blood samples (7 mL) were collected during each study period at Hour 0 (predose), and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24 hours postdose. A total of 48 blood samples (336 mL) were drawn during the study for drug analysis. Samples were collected and processed on an ice bath. Plasma samples were separated by centrifugation, frozen at -20°C, and kept frozen until assayed at

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Study Drug Administration

Dosing for each study period will be separated by a minimum 7-day washout interval.

	<u>Screen</u>	<u>Dose</u> <u>Period 1</u>	<u>Washout</u>	<u>Dose</u> <u>Period 2</u>	<u>Washout</u>	<u>Dose</u> <u>Period 3</u>
Study Days	-21 to -1	1	2 to 7	8	9 to 14	15

At Hour 0 on Day 1 of each study period, the subjects received one of three treatments.

- Treatment A: Famotidine 40 mg ODT tablets *with* water
- Treatment B: Famotidine 40 mg ODT tablets *without* water
- Treatment C: Pepcid® (famotidine) 40 mg tablets with water

Subjects randomized to Treatment A and B received a single oral dose of one 40 mg famotidine ODT tablet placed on the subject's tongue until disintegrated. The subject then was instructed to swallow the study drug mixture and then administered 240 mL of water for treatment A and without water for treatment B. Subjects randomized to Treatment C took the tablet with 240 mL of water.

A total of 30 subjects were enrolled. Each of the subjects were randomly assigned to one of six dosing sequences with 5 subjects per sequence group. Each of the groups will receive their assigned treatment according to the randomization schedule.

Sequence Group	Period 1	Period 2	Period 3
1 (N=5)	A	B	C
2 (N=5)	B	C	A
3 (N=5)	C	A	B
4 (N=5)	A	C	B
5 (N=5)	B	A	C
6 (N=5)	C	B	A

From sponsor's submission appendix 1.1

Study Population

Non-institutionalized volunteers consisting of college students and members of the community at large participated in the study.

Inclusion Criteria

- Non-tobacco-using (6 months minimum) males and females between

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- 19 and 50 years of age with voluntary consent.
- Female subjects must be surgically sterile, at least 2 years postmenopausal, or, if sexually active, must have a partner who has been vasectomized for at least 6 months, or agree to utilize acceptable methods of contraception.
- Body weight from 15% below or 15% above, inclusive, the ideal weight for height and frame as adapted from the 1983 Metropolitan Life Table as adapted from the 1983 Metropolitan Life Table.

Exclusion Criteria

- History of clinically significant organ system disease or any other condition that would jeopardize the safety of the subject or impact the validity of the study results.
- History of allergic or adverse response to famotidine or related drugs.
- Positive results from HIV antibody screen, hepatitis B surface antigen, and/or hepatitis C antibody screen.
- Participation in a previous clinical trial within 30 days prior to study initiation.
- Blood donation of blood or blood products within 30 days prior to or plasma donation within 7 days prior to study initiation.
- Difficulty in swallowing medication or any gastrointestinal disease/disorder that would affect the drug absorption.
- Abnormal diet or substantial changes in eating habits within 30 days prior to study initiation. An example of an abnormal diet would include, but not be limited to, vegetarian, fasting, liquid supplement, etc.
- Unwilling to eat the food as provided in the study menu.
- Treatment with any known enzyme-altering agents (barbiturates, phenothiazines, cimetidine, etc.) within 30 days prior to study initiation.
- Use of any prescription medication within 14 days prior to study initiation (with the exception of hormonal contraceptives for females).
- Use of any over-the-counter (OTC) medication within 7 days prior to study initiation.
- Positive urine screen for alcohol or drugs of abuse at screening and/or check-in.
- History of alcohol or drug abuse within the 2 years prior to dosing.
- Any presence of phenylketonuria (PKU)

Concomitant Therapy

Prohibited

- Prescription medication for a period of at least 14 days prior

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to or during the study initiation (with the exception of hormonal contraceptives for females).

- Over-the-counter (OTC) medication, including mega-dose vitamins, herbal preparations, analgesics, and antacids, 7 days prior to or during each study treatment period.
- Foods or beverages containing alcohol or caffeine/xanthine, within 48 hours prior to or during each study treatment period.
- Tobacco/nicotine use for a minimum of 6 months prior to or during the study.

Pharmacokinetic and Statistical Methods

The following pharmacokinetic parameters were computed from the drug concentration-time data for famotidine using noncompartmental methods. Actual sample times were used for the determination of the pharmacokinetic parameters.

AUC(0-t) - Area under the drug concentration-time curve

AUC(0-inf) - Area under the drug concentration-time curve

AUC(0-t)/AUC(0-inf) - Ratio of AUC(0-t) to AUC(0-inf). Also referred to as AUCR

Kel - Terminal elimination rate constant

T_{1/2} - Elimination half-life calculated as $\ln(2)/K_{el}$

C_{max} - Maximum observed drug concentration

T_{max} - Time of the maximum drug concentration (obtained without interpolation).

Plasma famotidine concentrations were tabulated by nominal sample time, and were summarized by treatment using descriptive statistics. Mean famotidine concentrations versus time were plotted for each treatment on the same graph. Individual famotidine concentrations were plotted for each subject with the 3 treatments on the same graph.

Statistical analyses were performed for famotidine on all 28 subjects who completed the study.

Bioequivalence of famotidine with respect to the log-transformed (\ln) AUC(0-t), AUC(0-inf), and C_{max} was concluded if the 90% confidence interval of the ratio of the product means for each parameter fell within the range of 80% to 125%. The 90% confidence interval was obtained from the anti logs of the lower and upper bounds of the 90% confidence interval for the difference in the least-squares means of the \ln -transformed data.

Linear regressions were performed using at least three data points. Plasma concentration values below the lower limit of quantitation were reported as 0 and were treated as such for the purpose of pharmacokinetic analysis.

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Safety

Clinical laboratory tests (hematology, serum chemistry, urinalysis), physical examination (complete vital signs), and a 12-lead ECG were evaluated during the screening period and at study completion.

At each check-in, a blood sample was collected from all females for a serum pregnancy test, and a urine sample was collected from each participant for a urine drug screen.

Blood pressure and heart rate was measured prior to each dose.

The subjects was instructed to inform the study physician and/or nurse of any adverse events that occurs at any time during the study. Adverse events were recorded on the case report form provided.

If a subject is withdrawn from the study, the following safety data was obtained: adverse event evaluation, 12-lead EKG, physical examination, and laboratory (chemistry, hematology, and urinalysis).

Discontinuation Criteria

Subject Withdrawal/Removal

The subjects were advised that they are free to withdraw from the study at any time. The Investigator may remove a subject if he feels this action is in the best interest of the subject. When a subject withdraws from the study, all of the safety data normally required at the end of the study should be obtained, if possible.

Subjects experiencing adverse reactions were followed until the reaction has resolved. Appropriate supportive and/or definitive therapy was administered as required.

Neither subjects withdrawing from the study nor those removed by the Investigator were replaced unless the number drops below 24 and the sponsor requests replacement subjects.

Ethics

The study was conducted in accordance with the Declaration of Helsinki, applicable regulatory requirements and Good Clinical Practices.

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Results

Patient Characteristics

See table 1 for demographic information.

Table A-1: Demographic Information

Trait		Female	Male	Overall
Gender	Female	.	.	12
	Male	.	.	18
Race	Asian	.	1	1
	Caucasian	10	13	23
	European/Middle East	2	1	3
	Hispanic	.	3	3
Frame Size	Small	.	2	2
	Medium	7	14	21
	Large	5	2	7
Age	Mean	27	33	30
	S.D.	6	9	9
	Minimum	20	22	20
	Maximum	37	50	50
	N	12	18	30
Weight (lb)	Mean	129.8	176.2	157.6
	S.D.	20.8	17.5	29.6
	Minimum	100.0	142.0	100.0
	Maximum	171.0	201.0	201.0
	N	12.0	18.0	30.0
Height (in)	Mean	65.4	72.0	69.4
	S.D.	2.4	3.6	4.6
	Minimum	61.0	64.0	61.0
	Maximum	70.0	76.0	76.0
	N	12.0	18.0	30.0

Adapted from Sponsor's submission p.95

Medical Officer Comments: Females comprise 40% while males comprise 60% of the population. Seventy-six percent (76%) were Caucasians, 10% were European/Middle Eastern, 10% were Hispanics (all males) and 3% (1 male) was Asian. The overall mean age of the subjects was 30 years (range 20-50 years), and the mean weight was 157.6 pounds (range 100-201 pounds).

Patient Accounting

A total of 30 subjects (18 males and 12 females) were enrolled, and 28 subjects (18 males and 10 females) completed the study. Two subjects were discontinued/withdrawn from the study: subject 5 did not return for Period 3 due to a very sick child. Subject 8 was unhappy about the blood draws and requested to go home.

CLINICAL REVIEW

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Protocol Deviations

Subject 16 had an adverse event of white blood cells in urine. The subject did not return to the facility to give a urine sample after efforts were made to get the subject to return. The subject is considered lost to follow-up.

Results of Pharmacokinetic and Statistical Analyses

Table A-2: Summary of the Pharmacokinetic Parameters of Plasma Famotidine for Treatments A and C

Pharmacokinetic Parameters	Plasma Famotidine <i>Treatment A</i>		Plasma Famotidine <i>Treatment C</i>		90% CI	% Mean Ratio
	Arithmetic Mean	SD	Arithmetic Mean	SD		
C _{max} (ng/mL)	134.581	39.487	132.063	39.974		
T _{max} (hr)	2.37	0.929	2.25	1.03		
AUC (0-t) (ng*hr/mL)	892.72	207.31	858.23	231.81		
AUC (0-inf) (ng*hr/mL)	915.30	209.33	880.87	233.32		
T _{1/2} (hr)	4.89	0.660	5.16	1.01		
K _{e1} (1/hr)	0.144	0.0187	0.139	0.0253		
AUCR	0.975	0.00899	0.973	0.0123	-	
ln (C _{max})	4.859	0.3054	4.845	0.2750	93.61-109.85	101.4
ln[AUC(0-t)]	6.768	0.2359	6.719	0.2736	98.05-111.94	104.8
ln[AUC(0-inf)]	6.794	0.2340	6.747	0.2687	98.08-111.55	104.6

Treatment A = 1 x40 mg Famotidine ODT with water (test)

Treatment C = 1 x 40 mg Pepcid Tablet (reference)

Medical Officer Comments: The above table shows that when comparing Treatment A versus Treatment C, the mean ratios of famotidine log-transformed (*ln*) C_{max} was 101.4%, AUC(0-t) was 104.8%, and AUC(0-inf) was 104.6%. It appears that when administered with water, the test formulation resulted in a similar rate and extent of exposure to famotidine as the reference formulation. The 90% confidence intervals were all within the 80% to 125% range required for bioequivalence: ln (C_{max}), at 93.61%-109.85%, ln[AUC(0-t)], at 98.05% -111.94%, and ln[AUC(0-int)], at 98.08% -111.55%.

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Table A-3: Summary of the Pharmacokinetic Parameters of Plasma Famotidine for Treatments B and C

Pharmacokinetic Parameters	Plasma Famotidine				90% CI	% Mean Ratio
	Treatment B		Treatment C			
	Arithmetic Mean	SD	Arithmetic Mean	SD		
Cmax (ng/mL)	135.815	39.249	132.063	39.974		
Tmax (hr)	2.62	0.890	2.25	1.03		
AUC (0-t) (ng*hr/mL)	884.48	212.28	858.23	231.81		
AUC (0-inf) (ng*hr/mL)	905.98	212.70	880.87	233.32		
T1/2(hr)	4.99	0.704	5.16	1.01		
Kel(1/hr)	0.142	0.0208	0.139	0.0253		
AUCR	0.975	0.00892	0.973	0.0123		
ln(Cmax)	4.870	0.2940	4.845	0.2750	94.73-111.16	102.6
ln[AUC(0-t)]	6.755	0.2544	6.719	0.2736	97.10-110.86	103.8
ln{AUC(0-inf)}	6.781	0.2489	6.747	0.2687	97.09-110.42	103.5

Treatment B = 1 x 40 mg Famotidine ODT without water (test)

Treatment C = 1 x 40 mg Pepcid Tablet (reference)

Medical Officer Comments: This above table shows that when comparing Treatment A versus Treatment C, the mean ratios of famotidine ln-transformed Cmax was 102.6%, AUC(0-t) was 103.8%, and AUC(0-inf) was 103.5%. It appears that when administered without water, the test formulation resulted in a similar rate and extent of exposure to famotidine as the reference formulation. The 90% confidence intervals were all within the 80% to 125% range required for bioequivalence: ln (Cmax), at 94.73%-111.16%, ln[AUC(0-t)], at 97.10% -110.86%, and ln[AUC(0-int)], at 97.09% -110.42%.

The times to disintegration for each subject for each of the two treatments are presented in the following tables:

CLINICAL REVIEW

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Table A-4: Times to Disintegration of Famotidine ODT

Time to Disintegration (seconds)		
Subject	Treatment A (with water)	Treatment B (without water)
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
27		
28		
29		
30		
Mean	72.97	80.30
SD	41.10	36.62
Minimum	—	—
Median	59.00	67.00
Maximum	—	—
N	30.00	30.00

Adapted from Sponsor's submission p.091

Table A-5: Time to Disintegration in Seconds (Overall)

Mean	76.63
SD	38.77
Minimum	—
Median	62.50
Maximum	—
N	60.00

Adapted from Sponsor's submission p.092

CLINICAL REVIEW

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Medical Officer Comments: The mean disintegration time for Treatment A was 72.97 ± 41.10 seconds (range — secs) and for Treatment B was 80.30 ± 36.62 seconds (range — secs). The overall disintegration duration of 76.63 ± 38.77 seconds appears long when compared to the various available orally disintegrating products available on the market.

Safety

Adverse Events

Below is a table of adverse events (AEs) by WHOART preferred term and body system.

Table A-6: All Adverse Events

Body System Adverse Event	Famotidine 40 mg ODT (N = 60) n (%) {AEs}		Famotidine 40 mg Tablets (N = 28) n (%) {AEs}
	With water (N = 30)	Without water (N = 30)	
Subjects with at least one AE	5 (16.7) {11}	5 (16.7) {9}	2 (7.1) {2}
<i>Body as a whole, general</i>			
Fever	1 (1.7) {1}	0	0
<i>Central & peripheral nervous</i>			
Headache	0	0	2 (7.1) {2}
Dizziness	1 (1.7) {1}	0	0
<i>Gastrointestinal</i>			
Nausea	2 (3.3) {2}	1 (1.7) {1}	0
Diarrhea	1 (1.7) {1}	0	0
Dyspepsia	1 (1.7) {1}	0	0
Vomiting	1 (1.7) {1}	0	0
<i>Liver & biliary</i>			
SGPT increased	0	1 (1.7) {1}	0
<i>Musculoskeletal</i>			
Back pain	1 (1.7) {1}	0	0
<i>Red blood cell</i>			
Anemia	(1.7) {1}	1 (1.7) {2}	0
<i>Reproductive, female</i>			
Dysmenorrhea	(1.7) {1}	0	0
<i>Resistance mechanism</i>			
Herpes simplex	1 (1.7) {1}	0	0
<i>Urinary</i>			
Urine abnormal	0	2 (3.3) {3}	0
Hematuria	0	1 (1.7) {1}	0
Pyuria	0	1 (1.7) {1}	0

Adapted from sponsor's submission p.295

n = number of subjects with the AE

(AEs) = number of AEs reported

A subject may have had more than one AE

CLINICAL REVIEW

Clinical Review Section

A total of 10 subjects (16.7%) in the Famotidine ODT group had 20 AEs while two (7.1%) subjects in the Famotidine Tablet group had two (2) AEs. The safety profile of Famotidine ODT was not different whether the ODT was administered with or without water.

There were no reported AEs that were severe in intensity. In the Famotidine 40 mg ODT group, 13 AEs (65%) were mild and 7 AEs (35%) were moderate in intensity. In the Famotidine 40 mg Tablet group one AE (50%) was mild and one AE (50%) was moderate in intensity.

All adverse events fully resolved except for one. One subject had an abnormal urinalysis (pyuria); on recheck, bacteria in the urine had resolved but white blood cells were still present. The subject did not return for a second recheck; therefore the outcome is unknown.

The table below is a summary of considered treatment-related adverse events.

Table A-7: Treatment Related Adverse Events

Body System Adverse Event	Famotidine 40mg ODT (N=60) n (%)	Famotidine 40mg Tablets (N=60) n (%)
Central & Peripheral Nervous <i>Dizziness</i>	1 (1.7)	0
Gastrointestinal <i>Nausea</i> <i>Dyspepsia</i>	2 (3.3) 1 (1.7)	0 0
Liver & Biliary <i>SGOT increased</i>	1 (1.7)	0

Adapted from sponsor's submission p. 236

The following four (4) subjects in the famotidine ODT group had AEs that were considered treatment related: subject #8 experienced moderate lightheadedness and moderate nausea, subject #12 had nausea, subject #15 had dyspepsia, subject #19 had elevated SGPT (ALT) of 52 U/L. These were all considered to be mild in intensity.

There were no deaths, serious adverse events nor other significant AEs that occurred during the trial. No withdrawals due to adverse events occurred during the trial.

This study shows that famotidine 40mg ODT has a similar safety profile when compared to the referenced listed drug, Pepcid 40mg tablets. For famotidine ODT, the most common treatment related AE was nausea (3.3%). In controlled clinical trials with Pepcid tablets, the adverse reactions reported in more than 1% of patients on therapy that maybe causally related to the drug were headache (4.7%), dizziness (1.3%), diarrhea (1.7%), and constipation (1.2%).

CLINICAL REVIEW

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Dyspepsia was the only AE considered possibly related to famotidine ODT that has not been reported with famotidine, unspecified "liver enzyme abnormalities" have been associated with Pepcid as described in the package insert. Famotidine ODT have a safety profile similar to the established safety profile of marketed Pepcid tablets. The risk associated with famotidine ODT are not expected to be different from the risks associated with marketed Pepcid tablets.

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/s/

Lolita Lopez
8/20/04 10:29:56 AM
MEDICAL OFFICER

Ruyi He
8/20/04 12:44:21 PM
MEDICAL OFFICER

I concur with Dr. Lopez's evaluation and recommendations.

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG
PRODUCTS**

MEDICAL OFFICER'S REVIEW

NDA: 21-712

Sponsor: Schwarz Pharma

Drug Name: Fluxid (famotidine orally disintegrating tablets)
20 and 40 mg

Indication: Short-term treatment and maintenance therapy of
acid related GI disorders

Drug Class: H₂ Receptor Antagonist

Documents Reviewed: Pediatric Study Waiver Request

Division Director: Robert Justice, M.D., M.S.

Deputy Director: Joyce Korvick, M.D., M.P.H.

Team Leader: Ruyi He, M.D.

Medical Officer: Lolita A. Lopez, M.D.

I. BACKGROUND

The sponsor, Schwarz Pharma is seeking for the approval of Fluxid™ (famotidine) orally disintegrating tablets 20 and 40 mg, NDA 21-712, submitted under a 505(b)(2) application relying on the Agency's previous findings of safety and efficacy for Merck's Pepcid Tablets (NDA 19-462). Pepcid™ is indicated for the treatment of duodenal and gastric ulcer, gastroesophageal reflux disease, and pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas). There are no proposed changes to the indications and administration schedule. In support of the NDA 21-712, a fasting single dose bioequivalence study was conducted comparing the approved Pepcid™ tablets 40 mg and Fluxid™ 40 mg orally disintegrating tablet (ODT).

In response to the Agency's request to provide either pediatric development plan or request for a waiver, the sponsor submitted a pediatric assessment and request for full waiver of pediatric studies. The sponsor states that a full waiver is justified because

the current labeling of the referenced listed drug (RLD) adequately addresses pediatric dosing information to treat GERD with or without esophagitis including erosions and ulcerations in pediatric patients

II. COMMENTS

The approved Merck's Pepcid™ products have a common package insert (PI) for the suspension, tablets, and injectable formulations. Pepcid™ (oral) is used in the pediatric population for the following indications and dosage:

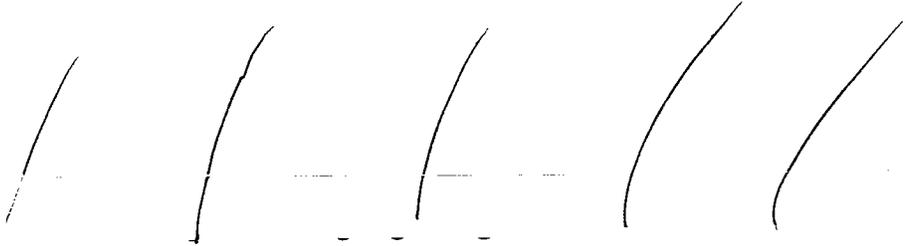
- **Treatment of peptic ulcer disease (duodenal ulcer or gastric ulcer)**
The suggested starting dose is 0.5 mg/kg/day PO at bedtime or 0.25 mg/kg PO twice daily. Maximum dosage is 40 mg/day.
- **Gastroesophageal reflux disease (GERD) with or without esophagitis**
Adolescents and children: The suggested starting dose is 0.5 mg/kg PO twice daily up to 40 mg PO twice daily. Maintenance dose and duration of therapy have not been determined in this age group. Doses up to 2 mg/kg/day PO have been used for GERD with or without esophagitis including erosions and ulcerations.
Infants 3 months to < 1 year: 0.5 mg/kg PO twice daily for up to 8 weeks in addition to conservative measures such as thickened feedings.
Infants < 3 months: 0.5 mg/kg PO once daily of the oral suspension for up to 8 weeks in addition to conservative measures such as thickened feedings.

Maximum Dosage Limits:

Children and adolescents: 2 mg/kg/day PO, usually not to exceed 40 mg/day PO, 40 mg/day PO for GERD; 80 mg/day PO for esophagitis.

Infants 3 months to < 1 year: 1 mg/kg/day PO.

Infants < 3 months: 0.5 mg/kg/day PO.



III. RECOMMENDATION

This reviewer recommends that a full waiver for pediatric studies be granted to the sponsor because there are other age appropriate formulation (such as suspension) for famotidine products available on the market that adequately addresses pediatric dosing information.

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/s/

Lolita Lopez
7/16/04 04:39:29 PM
MEDICAL OFFICER

Ruyi He
7/16/04 04:49:25 PM
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