

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-712

PHARMACOLOGY REVIEW(S)



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-712
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	11/25/03
PRODUCT:	Famotidine Orally Disintegrating Tablets
INTENDED CLINICAL POPULATION:	Patients with Acid Related Gastrointestinal Disorders
SPONSOR:	Schwarz Pharma
DOCUMENTS REVIEWED:	Vol. 8-10
REVIEW DIVISION:	Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
PHARM/TOX REVIEWER:	Ronald Honchel, Ph.D,
PHARM/TOX SUPERVISOR:	Jasti B. Choudary, B.V.Sc., Ph.D.
PROJECT MANAGER:	Betsy Scroggs, Pharm.D.

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

The application is recommended for approval.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

The proposed labeling for famotidine ODT was based on an ODT originally approved for Pepcid that was discontinued by Merck and is no longer available on the marketplace. From a preclinical standpoint, some minor changes are recommended (see pages 7-10) in order to follow present labeling patterns.

II. Summary of nonclinical findings

A. Brief overview of Toxicological findings

Famotidine was generally well tolerated in animal toxicology studies. Rats tolerated oral repeat dose up to 2000 mg/kg b.i.d. for 13 weeks, and 1000 mg/kg/day for both 26 weeks and one year. The only finding consistently noted was eosinophilic cytoplasmic granularity in rat gastric chief cells in high dose animals that was shown to be reversible. Dogs tolerated oral repeat doses of up to 1000 mg/kg/day for 13 weeks and 500 mg/kg/day for one year. No consistent findings of toxicity were observed in dog studies. Famotidine did not enhance tumorigenic potential in mouse or rat 2-year carcinogenicity studies. Famotidine was negative in standard genotoxic assays. Famotidine did not affect reproduction or fertility, and was not teratogenic.

B. Pharmacologic activity

Famotidine was shown to be a potent and selective competitive histamine H₂ receptor antagonist that suppressed gastric acid secretion in various rat and dog *in vivo* models with the oral antisecretory ED₅₀ ranging from 0.01 to 0.45 mg/kg. Famotidine also inhibited gastric ulcer formation in a number of rat (the ED₅₀ ranged from 0.03 to 0.6 mg/kg) *in vivo* models. No cardiovascular or ECG effects were apparent in dogs after a single oral dose of 30 mg/kg. Oral administration of 100 mg/kg famotidine had no effect on locomotion or rotarod performance in mice, thiopental-induced sleeping time in mice, hexobarbital-induced sleeping time in rats, or pentetrazole-induced seizures in mice.

C. Nonclinical safety issues relevant to clinical use

None.

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ON ORIGINAL**

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ON ORIGINAL**

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-712

Review number: 01

Sequence number/date/type of submission: 000/November 24, 2003/initial submission

Information to sponsor: Yes (X) No ()

Sponsor and/or agent: Schwarz Pharma, Inc., Mequon, WI

Manufacturer for drug substance: _____

Reviewer name: Ronald Honchel, Ph.D.

Division name: Division of Gastrointestinal and Coagulation Drug Products

HFD #: 180

Review completion date: September 1, 2004

Drug:

Trade name: Pepcid

Generic name: Famotidine

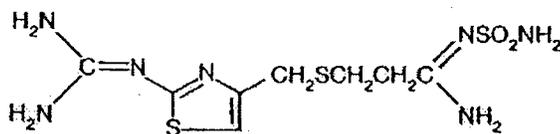
Code name: MK-208

Chemical name: N-(aminosulfonyl)-3-[[[2-[Aminoiminoethyl]amino]-4-thiazolyl]methyl]thio-propanimidamide; 1-Amino-3-[[[2-(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propylidene] sulfamide

CAS registry number: 76824-35-6

Molecular formula/molecular weight: C₈H₁₅N₇O₂S₃/337.45

Structure:



Relevant INDs/NDAs/DMFs: NDA 19-462 (Pepcid®; Merck, Sharpe and Dohme)

Drug class: Histamine H₂ receptor antagonist

Intended clinical population: Patients with acid-related gastrointestinal disorders.

Indications: Famotidine ODT is intended for the short-term treatment of active duodenal and gastric ulcers (40 mg daily), long-term prevention of duodenal ulcer recurrence (20 mg daily), short-term treatment of gastroesophageal reflux disease (20 or

40 mg daily), and the long-term management of pathological hypersecretory conditions (dose adjusted to individual patient needs).

Clinical formulation: The 40 mg famotidine dose strength will contain the inactive ingredients listed in Table 1 below. The 20 mg tablet is compositionally proportional to the 40 mg tablet.

Table 1: Inactive Ingredients in the Proposed Schwarz Pharma Famotidine 40 mg Orally Disintegrating Tablet

Ingredient [CAS #]	Function	Formulation	
		(mg/tablet)	(%)
Hypromellose			
Magnesium Stearate,			
Mannitol			
Sucralose	Sweetener		
Crospovidone			
Sodium Bicarbonate			
Citric Acid			
Microcrystalline Cellulose			
Colloidal Silicon Dioxide			
Natural and Artificial Cherry Flavor	Flavor		

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: No preclinical studies were submitted.

Studies not reviewed within this submission: None.

2.6.2 PHARMACOLOGY

None submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

No preclinical studies were submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

None submitted.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

No preclinical studies were submitted.

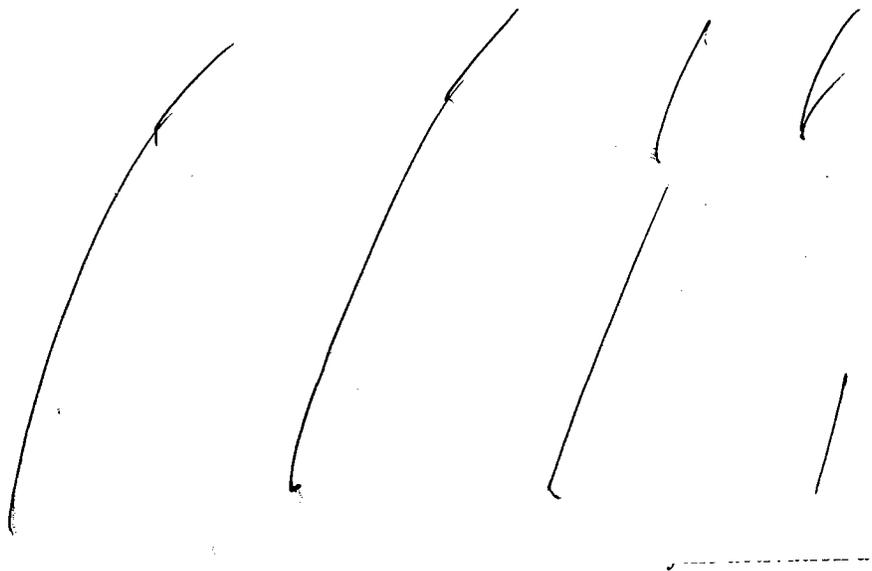
2.6.6 TOXICOLOGY

None submitted.

2.6.7 TOXICOLOGY TABULATED SUMMARY

No preclinical studies were submitted.

LABELING



3 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

SUMMARY AND EVALUATION

No preclinical studies were submitted in this application. The sponsor relies on the Agency's findings of safety and efficacy for conventional immediate-release famotidine tablets originally approved under NDA 19-462, Merck's Pepcid® Tablets for this 505(b)(2) submission.

Famotidine is a histamine H₂ receptor antagonist that produces anti-secretory effects in regards to gastric acid secretion. Famotidine was shown to have high affinity to, and be highly selective for, H₂-histamine receptors in receptor binding assays. The anti-secretory activity of famotidine was demonstrated by the inhibition of both histamine-induced and vagal or field-stimulated acid secretion in mouse isolated whole stomach. The potential efficacy of orally administered famotidine was demonstrated by the inhibition of gastric acid secretion in various rat and dog *in vivo* models. Famotidine also inhibited gastric ulcer formation in a number of rat *in vivo* models. No tolerance to the gastric anti-secretory effect of famotidine was observed after chronic administration. Unlike cimetidine, famotidine does not alter the binding of testosterone to the androgen receptor.

The bioavailability of orally administered famotidine was around 30-40% in rats, dogs and humans. The half-life in rats, dogs and humans was approximately 1.9, 3 and 3 hours, respectively, and the T_{max} was 2, 3 and 2 hours, respectively. Famotidine did not show a tendency for accumulation in repeat-dose studies. After single dose oral treatment, levels of famotidine were highest in the rat gastrointestinal tract followed by the kidneys, liver, submandibular gland and pancreas. No drug was present by 24 hours post dose. Only traces of drug were found in fetal tissues after administration of famotidine to pregnant rats, although significant amounts of drug were detected in the milk. Protein binding was approximately 21% to 27% for rats, dogs and humans. Famotidine metabolism was similar in rats, dogs and humans with approximately 80 % of the absorbed dose excreted unchanged. The remaining 20% was metabolized to an S-oxide by a sulfoxxygenase present in a number of tissues. Both the unchanged compound and S-oxide metabolite are excreted primarily via the urine. Famotidine demonstrated significantly less binding to cytochrome P450 than cimetidine and produced minimal inhibition in various *in vitro* and *in vivo* cytochrome P450 enzyme assays.

Single oral doses of up to 3000 mg/kg in rats and mice and 2000 mg/kg in dogs were not lethal.

Other than a dose- and time-dependent increase in incidence and severity of eosinophilic cytoplasmic granularity of the chief cells, no changes of toxicological significance were observed in 13-week, 26-week and 52 week rat oral toxicity studies at daily doses up to 4000, 1000, and 2000 mg/kg/day, respectively. Eosinophilic cytoplasmic granularity of chief cells was found to be reversible in a 26-week treatment/14-week recovery study. Other than slight body weight loss in high dose groups, no significant toxicological

changes were observed in 30-day, 13-week, and 52-week dog oral toxicity studies at daily doses up to 4000, 1000, and 500 mg/kg/day, respectively.

In a 106-week and a 92-week study in rats and mice, respectively, there was no evidence of carcinogenic potential at oral doses of up to 2000 mg/kg/day famotidine.

Famotidine was negative in the Ames test, the mouse micronucleus test and the mouse chromosomal aberration test.

Fertility and reproductive performance were not affected in studies with rats given oral doses up to 2000 mg/kg/day. Famotidine was not fetotoxic or teratogenic at doses up to 2000 mg/kg/day in rats and 500 mg/kg/day in rabbits.

In special toxicology studies, famotidine: 1) had no effect in thyroid function tests in male rats; 2) did not protect against or potentiate acetaminophen-induced hepatic injury in male rats or inhibit liver regeneration in female rats; 3) did not induce IgE antibody production in a guinea pig or mouse models of immunogenicity; and 4) was not irritating to the rabbit eye, rabbit muscle or dog muscle.

The Sponsor's drug product is a new formulation of famotidine. Famotidine was adequately tested in previous preclinical studies cited in NDA 19-462 and published literature included in this submission. The dose strengths for the new orally disintegrating form are the same (20 and 40 mg) as the approved conventional tablets and will be labeled for the same indications and the same administration schedule as the conventional tablet. The Sponsor presented pharmacokinetic data from healthy human volunteers that received Famotidine 40 mg ODTs or Pepcid 40 mg tablets. Famotidine was shown to be bioequivalent to Pepcid with nearly identical C_{max}, T_{max}, t_{1/2}, and AUC values. Except for natural and artificial cherry flavor and sucralose, the inactive ingredients for famotidine ODT are listed on FDA's Inactive Ingredient list. These inactive ingredients are commonly used in oral tablet formulations and have a long and safe history of use in pharmaceutical preparations. The natural and artificial cherry flavors are common food flavoring ingredients and have FDA "generally regarded as safe (GRAS)" status. Sucralose is a FDA approved food additive sweetener. The maximum patient exposure to sucralose if given the recommended maximum human dose (40 mg) of famotidine would be — mg/kg/day (assuming 50 kg body weight) and the acceptable daily intake (ADI) for sucralose is 5 mg/kg/day. Therefore, the formulation should be safe in regards to inactive ingredients.

RECOMMENDATIONS:

From a preclinical viewpoint, the application is recommended for approval with a provision that the labeling be changed as described in the "Labeling" section.

Unresolved toxicology issues: None.

Ronald Honchel, Ph.D.
Pharmacologist, HFD-180

Date

Comment:

Jasti B. Choudary, B.V.Sc., Ph.D. Date
Supervisory Pharmacologist, HFD-180

cc:
IND
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Honchel
R/D Init. J. Choudary 8/13/04

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/s/

Ronald Honchel
9/3/04 10:37:34 AM
PHARMACOLOGIST

Jasti Choudary
9/3/04 01:14:02 PM
PHARMACOLOGIST