

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-712**

**CHEMISTRY REVIEW(S)**

**NDA 21-712**

**Fluxid<sup>®</sup> (famotidine) Orally Disintegrating Tablets, 20 mg  
and 40 mg**

**Schwarz Pharma, Inc.**

**Raymond P. Frankewich, Ph.D.  
Division of GI and Coagulation Drug Products (HFD-180)**

# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>3</b>
<b>The Executive Summary .....</b>	<b>8</b>
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability .....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s) .....	8
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block .....	9
<b>Chemistry Assessment .....</b>	<b>10</b>
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	NA
S DRUG SUBSTANCE .....	10
P DRUG PRODUCT .....	10
A APPENDICES .....	NA
R REGIONAL INFORMATION .....	NA
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....	NA
A. Labeling & Package Insert .....	NA
B. Environmental Assessment Or Claim Of Categorical Exclusion .....	NA
III. List Of Deficiencies To Be Communicated.....	NA



# Chemistry Review Data Sheet

1. NDA 21-712
2. REVIEW #: 2
3. REVIEW DATE: September 21, 2004
4. REVIEWER: Raymond P. Frankewich, Ph.D.

## 5. PREVIOUS DOCUMENTS:

Previous Documents

NDA

Document Date

November 24, 2003

## 6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

NDA

Document Date

November 24, 2003

March 10, 2004

July 20, 2004

August 27, 2004

September 14, 2004



## Chemistry Review Data Sheet

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Schwarz Pharma, Inc.  
6140 W. Executive Drive  
Mequon, WI 53902

Address: Mailing:  
P. O. Box 2038  
Milwaukee, WI 53201-2038

Representative: Donna K. Multhauf, Director, Regulatory Affairs

Telephone: 262-238-5225

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Fluxid<sup>®</sup>
- b) Non-Proprietary Name (USAN): Famotidine
- c) Code Name/# (ONDC only): NA
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Pepcid<sup>®</sup> (Famotidine) Tablets, USP (NDA 19-462); Pepcid<sup>®</sup> RPD<sup>®</sup> (Famotidine) Tablets (NDA 20-752); Pepcid<sup>®</sup> AC<sup>®</sup> Acid Controller (Famotidine) Non-prescription Chewable Tablets (NDA 20-801); Pepcid<sup>®</sup> AC<sup>®</sup> (Famotidine) Coated Tablets (NDA 20-902).

10. PHARMACOL. CATEGORY: Antagonist to Histamine H<sub>2</sub> Receptors

11. DOSAGE FORM: Tablet, Orally Disintegrating (Tab Orally Dis, Code 522)

12. STRENGTH/POTENCY: 20 mg, 40 mg

13. ROUTE OF ADMINISTRATION: Oral

Chemistry Review Data Sheet

14. Rx/OTC DISPENSED:       X   Rx          OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

     SPOTS product – Form Completed

  X   Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
✓	II	✓	Famotidine (drug substance)	1	Adequate	8/04	LOA pg. 015, vol. 1.1, dated 4/28/03.
	III			3	Adequate	9/26/01	LOA pg. 012 of vol. 1.1, dated 12/9/02
	III			1	Adequate	8/04	LOA pg. 019, vol. 1.1, dated 11/12/02
	III			3	Adequate	4/9/04	LOA pg. 016 v. 1.1, dated 3/27/03.
	III			3	Adequate	8/3/01	LOA pg. 011 v. 1.1, dated 10/21/02.
	III			1	Adequate	8/04	LOA pg. 013 v. 1.1, dated 2/3/03.
	III			1	Adequate	8/04	LOA pg. 010 v. 1.1, dated 1/24/03.
✓	IV	✓		1	Adequate	8/04	LOA pg. 020 v. 1.1, dated 11/12/03.

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

### 18. STATUS:

#### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	None	-	-
EES	Acceptable	26-7-2004	J. D'Ambrogio (HFD-324)
Pharm/Tox	None	-	-
Biopharm	Changes to Specification and Labeling	13-7-2004	Tien-Mien Chen
	Acceptable	16-9-2004	
LNC	None	-	-
Methods Validation	Pending	21-9-2004	Frankewich
OPSS/DMETS	Acceptable	20-9-2004	L. Wisniewski
EA	Acceptable/Exempt	5-8-2004	Frankewich
Microbiology	None	-	-



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

### 19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. \_\_\_\_ Yes \_\_\_\_ No If no, explain reason(s) below:

**APPEARS THIS WAY  
ON ORIGINAL**

# The Chemistry Review for NDA 21-712

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Recommended for Approval; see Section II.C. below.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance is famotidine, which has been marketed as an active substance in several drug products since 1986. Famotidine is described in USAN as an Antagonist to Histamine H<sub>2</sub> receptors. There is a USP monograph for Famotidine. Famotidine is described in DMF

Famotidine is the active ingredient in several other currently marketed drugs. This Drug Product is a tablet that is intended to disintegrate within the mouth (Orally Disintegrating Tablet, a. k. a. ODT). A ODT formulation of famotidine has been approved previously, but is no longer available commercially.

See discussion in Section P.5.2 of this review (pp. 35 - 37).

#### B. Description of How the Drug Product is Intended to be Used

Drug Product is intended primarily as a short-term or maintenance treatment for gastric or duodenal ulcers. It is also intended as a treatment of pathological hypersecretory conditions (e. g. Zollinger - Ellison syndrome). The maximum daily dose of famotidine that is proposed in this submission is for the treatment of pathological hypersecretory conditions.

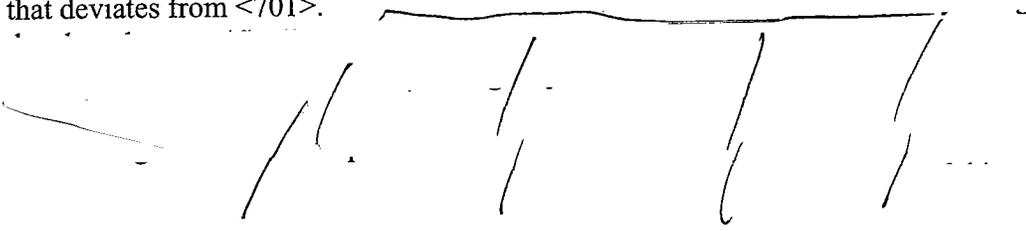
#### C. Basis for Approvability or Not-Approval Recommendation

In CMC review #1 of this NDA, it was asserted that two issues should be resolved before this application may be approved. The first was the status of impurities eluting at \_\_\_\_\_ in the Determination of Related Substances by HPLC (see section P.5.2 of CMC Review #1, pg. 50). The applicant has provided information and interpretation regarding the molecular structure and potential for toxicity of these

**Executive Summary Section**

compounds (see discussion below under Responses to Comments in IR Letter Dated July 26, 2004, Drug Product section, no. 20 and no. 22). Complete or partial structures of the compounds are provided. These impurities are monitored in the Drug Product Specification for release and stability, with the test for Any Single Other Impurity. The information provided by the applicant demonstrates that this test and its acceptance criterion (NMT — of the Drug Substance) is appropriate.

The second of the two issues was the analytical procedure and acceptance criterion for Disintegration Time. 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 °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.

An expiration period of 24 months for the drug product in all the proposed packaging configurations appears to be justified by the stability data. See discussion under no. 21 of the July 26, 2004 Information Request Letter.

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

**C. CC Block**

21 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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

/s/  
-----

Ray Frankewich  
9/21/04 06:01:49 PM  
CHEMIST

Liang Zhou  
9/22/04 10:10:44 AM  
CHEMIST

**NDA 21-712**

**Fluxid<sup>®</sup> (famotidine) Orally Disintegrating Tablets, 20 mg  
and 40 mg**

**Schwarz Pharma, Inc.**

**Raymond P. Frankewich, Ph.D.  
Division of GI and Coagulation Drug Products (HFD-180)**



# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>3</b>
<b>The Executive Summary .....</b>	<b>8</b>
<b>I. Recommendations.....</b>	<b>8</b>
A. Recommendation and Conclusion on Approvability .....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
<b>II. Summary of Chemistry Assessments.....</b>	<b>8</b>
A. Description of the Drug Product(s) and Drug Substance(s) .....	8
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
<b>III. Administrative.....</b>	<b>9</b>
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block .....	9
<b>Chemistry Assessment .....</b>	<b>10</b>
<b>I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....</b>	<b>10</b>
S DRUG SUBSTANCE [Name, Manufacturer] .....	10
P DRUG PRODUCT [Name, Dosage form].....	16
A APPENDICES .....	54
R REGIONAL INFORMATION .....	54
<b>II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .....</b>	<b>54</b>
A. Labeling & Package Insert .....	54
B. Environmental Assessment Or Claim Of Categorical Exclusion .....	59
<b>III. List Of Deficiencies To Be Communicated.....</b>	<b>59</b>



# Chemistry Review Data Sheet

1. NDA 21-712
2. REVIEW #: 1
3. REVIEW DATE: August 5, 2004
4. REVIEWER: Raymond P. Frankewich, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

NDA

Document Date

November 24, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

NDA

Document Date

November 24, 2003

March 10, 2004

July 20, 2004



## Chemistry Review Data Sheet

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Schwarz Pharma, Inc.  
6140 W. Executive Drive  
Mequon, WI 53902

Address: Mailing:  
• P. O. Box 2038  
Milwaukee, WI 53201-2038

Representative: Donna K. Multhauf, Director, Regulatory Affairs

Telephone: 262-238-5225

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Fluxid<sup>®</sup>
- b) Non-Proprietary Name (USAN): Famotidine
- c) Code Name/# (ONDC only): NA
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Pepcid<sup>®</sup> (Famotidine) Tablets, USP (NDA 19-462); Pepcid<sup>®</sup> RPD<sup>®</sup> (Famotidine) Tablets (NDA 20-752); Pepcid<sup>®</sup> AC<sup>®</sup> Acid Controller (Famotidine) Non-prescription Chewable Tablets (NDA 20-801); Pepcid<sup>®</sup> AC<sup>®</sup> (Famotidine) Coated Tablets (NDA 20-902).

10. PHARMACOL. CATEGORY: Antagonist to Histamine H<sub>2</sub> Receptors

11. DOSAGE FORM: Tablet, Orally Disintegrating (Tab Orally Dis, Code 522)

12. STRENGTH/POTENCY: 20 mg, 40 mg

13. ROUTE OF ADMINISTRATION: Oral



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

14. Rx/OTC DISPENSED:       X   Rx          OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

     SPOTS product – Form Completed

  X   Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
/	II	/	Famotidine (drug substance)	1	Adequate	8/04	LOA pg. 015, vol. 1.1, dated 4/28/03.
/	III	/		3	Adequate	9/26/01	LOA pg. 012 of vol. 1.1, dated 12/9/02
/	III	/		1	Adequate	8/04	LOA pg. 019, vol. 1.1, dated 11/12/02
/	III	/		3	Adequate	4/9/04	LOA pg. 016 v. 1.1, dated 3/27/03.
/	III	/		3	Adequate	8/3/01	LOA pg. 011 v. 1.1, dated 10/21/02.
/	III	/		1	Adequate	8/04	LOA pg. 013 v. 1.1, dated 2/3/03.
/	III	/		1	Adequate	8/04	LOA pg. 010 v. 1.1, dated 1/24/03.
/	IV	/		1	Adequate	8/04	LOA pg. 020 v. 1.1, dated 11/12/03.

**Chemistry Review Data Sheet**<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

**18. STATUS:****ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	None	-	-
EES	Acceptable	26-7-2004	J. D'Ambrogio (HFD-324)
Pharm/Tox	None	-	-
Biopharm	Changes to Specification and Labeling	7-13-2004	Tien-Mien Chen
LNC	None	-	-
Methods Validation	Pending	4-8-2004	Frankewich
OPSS/DMETS	Pending	4-2-2004 (Consult date)	-
EA	Acceptable/Exempt	5-8-2004	Frankewich
Microbiology	None	-	-



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

**OGD:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

**19. ORDER OF REVIEW (OGD Only)**

The application submission(s) covered by this review was taken in the date order of receipt. \_\_\_ Yes \_\_\_ No If no, explain reason(s) below:

**APPEARS THIS WAY  
ON ORIGINAL**

# The Chemistry Review for NDA 21-712

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Approvable; see Section II.C. below. Further communications with the firm to resolve the remaining issues are planned.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None at this time.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance is famotidine, which has been marketed as an active substance in several drug products since 1986. Famotidine is described in USAN as an Antagonist to Histamine H<sub>2</sub> receptors. There is a USP monograph for Famotidine. Famotidine is described in DMF

Famotidine is the active ingredient in several other currently marketed drugs. This Drug Product is a tablet that is intended to disintegrate within the mouth (Orally Disintegrating Tablet, a. k. a. ODT). A ODT formulation of famotidine has been approved previously, but is no longer available commercially.

#### B. Description of How the Drug Product is Intended to be Used

Drug Product is intended primarily as a short-term or maintenance treatment for gastric or duodenal ulcers. It is also intended as a treatment of pathological hypersecretory conditions (e. g. Zollinger - Ellison syndrome). The maximum daily dose of famotidine that is proposed in this submission is for the treatment of pathological hypersecretory conditions.

#### C. Basis for Approvability or Not-Approval Recommendation

Two issues should be resolved before this application may be approved. The first is the status of impurities eluting at \_\_\_\_\_ in the Determination of Related Substances by HPLC (see section P.5.2 of this review, pg. 50). It is anticipated that the applicant will provide information to adequately characterize these substances, provide

**Executive Summary Section**

data on their potential toxicity if necessary, and will establish specific acceptance criteria for their control if necessary. This issue is important because impurities which appear during the course of stability analyses are, in most cases, degradation products, which should be monitored. The second of the two issues is the analytical procedure and acceptance criterion for Disintegration Time. In the review (pg. 35 - 36) it is 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>.



**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

ChemistName/Date: Same date as draft review  
ChemistryTeamLeaderName/Date  
ProjectManagerName/Date

**C. CC Block**

53 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

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

/s/  
-----

Ray Frankewich  
8/5/04 07:03:57 PM  
CHEMIST

Liang Zhou  
8/6/04 12:14:31 PM  
CHEMIST  
DR letter is needed see the end of the review.