CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75611

CHEMISTRY REVIEW(S)

DIVISION REVIEW SUMMARY

ANDA #: 75-611

DRUG NAME: Famotidine

FIRM: TorPharm (Apotex Corporation)

DOSAGE FORM: Tablet

STRENGTH: 20 mg, 40 mg

CGMP STATEMENT/EER STATUS: Acceptable; September 3, 1999

BIO STUDY: Acceptable; May 30, 1999

METHODS VALIDATION: Satisfactory, July 29, 1999

PACKAGING: Both strengths were packaged in 30s, 100s, and 1000s.

STABILITY: Three months accelerated and 24 months room temperature stability data for lot #FD8068 (20 mg) and #FD8069 (40 mg) support the proposed 24-month expiration date.

LABELING: Acceptable, May 11, 2000 and June 22, 2001

STERILIZATION VALIDATION: N/A

ANDA BATCH: ( ) tablets of each strength.

SOURCE OF NDS: The firm's source of drug substance is ( ) DMF ( ) was found adequate on October 24, 2000.

PROPOSED PRODUCTION BATCH: ( ) Tablets of each strength.

RECOMMENDATION: Approve

REVIEWER: Ijeoma N. Nnamani, Ph.D
DATE: July 6, 2001
SIGNATURE: /S/ 7/18/01

TEAM LEADER: Brenda T. Arnwine
DATE: July 11, 2001
SIGNATURE: /S/ 7/19/01

1. CHEMISTRY REVIEW # 1

2. ANDA # 75-611

3. NAME AND ADDRESS OF APPLICANT
TorPharm
U.S. Agent: Apotex Corporation
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061

4. LEGAL BASIS FOR ANDA SUBMISSION
The basis of this submission is the approved listed drug, Pepcid ® Tablets, 20 mg and 40 mg (NDA #19-462). Patent certification and exclusivity statements are included (pp 7 - 9).

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Famotidine

8. SUPPLEMENT PROVIDE FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
March 29, 1999: Original Submission
May 30, 1999: Biostudy Acceptable
July 29, 1999: Methods Validation by NE Regional Lab.

10. PHARMACOLOGICAL CATEGORY
H_2 Receptor Antagonist

11. Rx or OTC
Rx

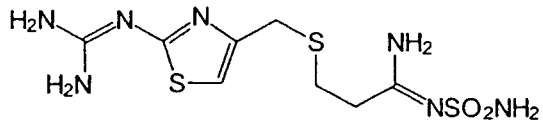
12. RELATED ANDA/DMFs
75-610

13. DOSAGE FORM
Tablet

14. POTENCY
20 mg & 40 mg

15. CHEMICAL NAME AND STRUCTURE

Famotidine. $C_8H_{15}N_7O_2S_3$. 337.45. *N*'-(aminosulfonyl)-3-[[[2-[(diaminoethylene)amino]-4-thiazolyl]methyl]thio] Propanimidamide.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
See review

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable, Major.

19. REVIEWER
Ijeoma N. Nnamani, Ph.D.

DATE COMPLETED
August 30, 1999

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Chem Review #1

SEP 10 1999

Chemistry comments to be provided to the applicant

ANDA: **75-611** APPLICANT: **TorPharm**

DRUG PRODUCT: Famotidine Tablets USP, 20 mg and 40 mg

The following deficiencies represent MAJOR deficiencies.

Deficiencies:

1. Related compounds of Famotidine have been identified and your chromatograms show that these impurities are eluting from the main peak, however, you identified them as unknown. Please revise and resubmit your COA including the identity of the related compounds and note that any unknown impurity should have a specification of NMT % (USP 23 General Notices and Requirements, Supplement 6, page 3636).

2. Famotidine has two known polymorphic forms. Please incorporate an identification test for the form in the drug substance, in addition to USP routine testings.

3. Your Unknown Compounds Quantitation Report and associated chromatograms (pp 1289 - 1294) show that impurities are separating from the main peak, however, you did not identify the impurity names, structures, and relative retention times.

4. We acknowledge the receipt of your In-process Sampling and Specifications (pp 1910 - 1917) in which you included a specification for . We recommend that be performed on all post-approval commercial production batches. Please change your statement on page 1656 and proposed specifications for to a mean of (% with a RSD %.

5. We were unable to locate some of your in-process test results such as( ) Sieve Analysis, Bulk and Tapped Density. Please resubmit.

6. Please include a specification for moisture in your finished product and stability specifications.

7. We recommend that known and unknown impurities be separated, rather than designating as "individual impurities." Please identify impurities as requested in comments 1 and 3, and include specifications for known, unknown, and total impurities in your release and stability specifications.

8. We note that you included the retention times for all your unknowns and the degradants resulting from subjecting the drug substance and product to different stress conditions, however, you failed to identify the impurities or degradants by name, structure, or relative retention times. These are needed to support the method.

9. We acknowledge the receipt of your memo dated September 4, 1998, (p 2344) in which you state that the USP Assay method for Famotidine tablets resulted in low recoveries and poor peak shape. Please submit the data referred to, and also submit the comparative data of samples of Pepcid® analyzed by your method and USP's method.

10. Please submit available updated room temperature stability data for the product.

11. It is noted that while on your stability protocol you indicated "any individual unknown impurities," on the stability data "largest unknown" is indicated." Please clarify.

12. What is your procedure for extending the expiration period?

13. Please state how you calculated your proposed expiration period of 24 months.

14. DMF was reviewed and the deficiencies found have been conveyed to the holder. These deficiencies should be answered satisfactorily before the application can be approved.

Sincerely yours,

/S/

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW # 2

2. ANDA # 75-611

3. NAME AND ADDRESS OF APPLICANT
TorPharm
U.S. Agent: Apotex Corporation
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061

4. LEGAL BASIS FOR ANDA SUBMISSION
The basis of this submission is the approved listed drug, Pepcid ® Tablets, 20 mg and 40 mg (NDA #19-462). Patent certification and exclusivity statements are included (pp 7 - 9).

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Famotidine

8. SUPPLEMENT PROVIDE FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
March 29, 1999: Original Submission
May 30, 1999: Biostudy Acceptable
July 29, 1999: Methods Validation by NE Regional Lab.
September 8, 1999: Chemistry Review # 1
October 7, 1999: Labeling Review # 1
November 10, 1999: Amendment

10. PHARMACOLOGICAL CATEGORY
H_2 Receptor Antagonist

11. Rx or OTC
Rx

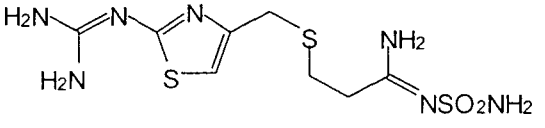
12. RELATED ANDA/DMFs
75-610

13. DOSAGE FORM
Tablet

14. POTENCY
20 mg & 40 mg

15. CHEMICAL NAME AND STRUCTURE

Famotidine. $C_8H_{15}N_7O_2S_3$. 337.45. *N'*-(aminosulfonyl)-3-[[[2-[(diaminoethylene)amino]-4-thiazolyl]methyl]thio] Propanimidamide.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
New deficiencies for this cycle are in bold.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable, Minor.

19. REVIEWER
Ijeoma N. Nnamani, Ph.D.

DATE COMPLETED
March 21, 2000

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Chem Review #2

38. Chemistry comments to be provided to the applicant

ANDA: **75-611** APPLICANT: **TorPharm**

DRUG PRODUCT: Famotidine Tablets USP, 20 mg and 40 mg

The following deficiencies represent MINOR deficiencies:

1. DMF is deficient and the holder has been informed.

2. Your CoA indicates Famotidine because of the melting point of the drug substance. Please include a quantitative specification of in your drug substance tests and specifications sheet and resubmit.

3. Revise and resubmit your finished product specifications and stability specifications to reflect your stability data. Your current specifications are high compared to your certificates of Analysis and stability data.

4. We acknowledge the receipt of your updated room temperature data. Please include individual named related compounds 1 to 9, moisture specification, and Q % in your stability report and resubmit.

5. Please submit updated room temperature data, if available.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW # 3

2. ANDA # 75-611

3. NAME AND ADDRESS OF APPLICANT
TorPharm
U.S. Agent: Apotex Corporation
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061

4. LEGAL BASIS FOR ANDA SUBMISSION
The basis of this submission is the approved listed drug, Pepcid ® Tablets, 20 mg and 40 mg (NDA #19-462). Patent certification and exclusivity statements are included (pp 7 - 9).

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Famotidine

8. SUPPLEMENT PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:
March 29, 1999: Original Submission
May 30, 1999: Biostudy Acceptable
July 29, 1999: Methods Validation by NE Regional Lab.
September 8, 1999: Chemistry Review # 1
October 7, 1999: Labeling Review # 1
November 10, 1999: Amendment
March 27, 2000: Chemistry Review #2
May 2, 2000: Amendment

10. PHARMACOLOGICAL CATEGORY
H_2 Receptor Antagonist

11. Rx or OTC
Rx

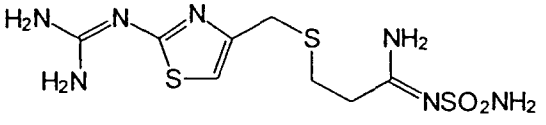
12. RELATED ANDA/DMFs
75-610

13. DOSAGE FORM
Tablet

14. POTENCY
20 mg & 40 mg

15. CHEMICAL NAME AND STRUCTURE

Famotidine. $C_8H_{15}N_7O_2S_3$. 337.45. *N'*-(aminosulfonyl)-3-[[[2-[(diaminoethylene)amino]-4-thiazolyl]methyl]thio] Propanimidamide.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
New deficiencies for this cycle are in bold/Italics.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable, Minor.

19. REVIEWER
Ijeoma N. Nnamani, Ph.D.

DATE COMPLETED
May 19, 2000

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Chem Review #3

JUN 26 2000

38. Chemistry comments to be provided to the applicant

ANDA: **75-611** APPLICANT: **TorPharm**

DRUG PRODUCT: Famotidine Tablets USP, 20 mg and 40 mg

The following deficiencies represent MINOR deficiencies:

1. DMF( ), is deficient and the holder has been informed.

2. We acknowledge your revisions to the drug substance, finished product, and stability specifications. Please include a limit for "Sum of Unknowns" rather than "report results." Also, Change "Total Impurities" to "Total Known and Unknown Impurities."

3. Please submit updated room temperature data, if available.

Sincerely yours,

/S/

for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW #4

2. ANDA # 75-611

3. NAME AND ADDRESS OF APPLICANT
TorPharm
U.S. Agent: Apotex Corporation
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061

4. LEGAL BASIS FOR ANDA SUBMISSION
The basis of this submission is the approved listed drug, Pepcid ® Tablets, 20 mg and 40 mg (NDA #19-462). Patent certification and exclusivity statements are included (pp 7 - 9).

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Famotidine

8. SUPPLEMENT PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:
March 29, 1999: Original Submission
May 30, 1999: Biostudy Acceptable
July 29, 1999: Methods Validation by NE Regional Lab.
September 8, 1999: Chemistry Review # 1
October 7, 1999: Labeling Review # 1
November 10, 1999: Amendment
March 27, 2000: Chemistry Review #2
May 2, 2000: Amendment
May 25, 2000: Chemistry Review #3
May 26, 2000: Deficiency Letter
June 9, 2000: Amendment

10. PHARMACOLOGICAL CATEGORY
H_2 Receptor Antagonist

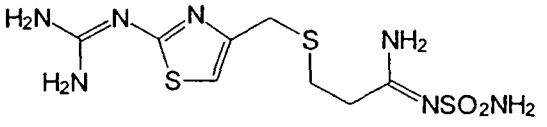
11. Rx or OTC
Rx

12. RELATED ANDA/DMFs
75-610

13. DOSAGE FORM
Tablet

14. POTENCY
20 mg & 40 mg

15. CHEMICAL NAME AND STRUCTURE
Famotidine. $C_8H_{15}N_7O_2S_3$. 337.45. *N*'-(aminosulfonyl)-3-[[[2-[(diaminoethylene)amino]-4-thiazolyl]methyl]thio] Propanimidamide.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
The only deficiency for this cycle is DMF.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable, Minor.

19. REVIEWER
Ijeoma N. Nnamani, Ph.D.

DATE COMPLETED
June 28, 2000

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Chem Review #4

JUL 26 2000

38. Chemistry comments to be provided to the applicant

ANDA: 75-611 APPLICANT: **TorPharm**

DRUG PRODUCT: Famotidine Tablets USP, 20 mg and 40 mg

The following deficiencies represent MINOR deficiencies:

1. DMF( ) is deficient and the holder has been informed.
2. Please submit a comparative impurity profile data of your drug product and the RLD.

Sincerely yours,

/S/

for Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW #5

2. ANDA # 75-611

3. NAME AND ADDRESS OF APPLICANT
TorPharm
U.S. Agent: Apotex Corporation
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061

4. LEGAL BASIS FOR ANDA SUBMISSION
The basis of this submission is the approved listed drug, Pepcid ® Tablets, 20 mg and 40 mg (NDA #19-462). Patent certification and exclusivity statements are included (pp 7 - 9).

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Famotidine

8. SUPPLEMENT PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:
March 29, 1999: Original Submission
May 30, 1999: Biostudy Acceptable
July 29, 1999: Methods Validation by NE Regional Lab.
September 8, 1999: Chemistry Review # 1
October 7, 1999: Labeling Review # 1
November 10, 1999: Amendment
March 27, 2000: Chemistry Review #2
May 2, 2000: Amendment
May 25, 2000: Chemistry Review #3
May 26, 2000: Deficiency Letter
June 9, 2000: Amendment
July 25, 2000: Chemistry Review #3
August 14, 2000: Amendment

10. PHARMACOLOGICAL CATEGORY
H_2 Receptor Antagonist

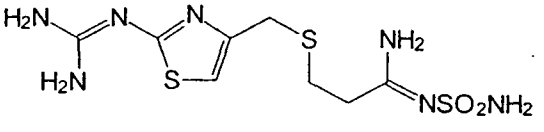
11. ℞ or OTC
℞

12. RELATED ANDA/DMFs
75-610

13. DOSAGE FORM
Tablet

14. POTENCY
20 mg & 40 mg

15. CHEMICAL NAME AND STRUCTURE
Famotidine. $C_8H_{15}N_7O_2S_3$. 337.45. *N'*-(aminosulfonyl)-3-[[[2-[(diaminoethylene)amino]-4-thiazolyl]methyl]thio] Propanimidamide.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
The only deficiency for this cycle is DMF.

18. CONCLUSIONS AND RECOMMENDATIONS
Not approvable, Minor Amendment.

19. REVIEWER
Ijeoma N. Nnamani, Ph.D.

DATE COMPLETED
October 13, 2000

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Chem Review #5

NOV 9 2000

38. Chemistry comments to be provided to the applicant

ANDA: 75-611 APPLICANT: **TorPharm**

DRUG PRODUCT: Famotidine Tablets USP, 20 mg and 40 mg

The following deficiency represents a MINOR deficiency:

Your DMF holder ( ) has proposed a new acceptance criteria and method of quantitation for the process impurity ( ) in the drug substance. We recommend that you contact ( ) then submit a revised Certificate of Analysis along with a method for the control of ( ).

Sincerely yours,

/S/

for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

1. CHEMISTRY REVIEW #6

2. ANDA # 75-611

3. NAME AND ADDRESS OF APPLICANT
Apotex Corporation
U.S. Agent: TorPharm
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite 127
Vernon Hills, Illinois 60061

4. LEGAL BASIS FOR ANDA SUBMISSION
The basis of this submission is the approved listed drug, Pepcid ® Tablets, 20 mg and 40 mg (NDA #19-462). Patent certification and exclusivity statements are included (pp 7 - 9).

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Famotidine

8. SUPPLEMENT PROVIDE FOR: N/A

9. AMENDMENTS AND OTHER DATES:
March 29, 1999: Original Submission
May 30, 1999: Biostudy Acceptable
July 29, 1999: Methods Validation by NE Regional Lab.
September 8, 1999: Chemistry Review # 1
October 7, 1999: Labeling Review # 1
November 10, 1999: Amendment
March 27, 2000: Chemistry Review #2
May 2, 2000: Amendment
May 25, 2000: Chemistry Review #3
May 26, 2000: Deficiency Letter
June 9, 2000: Amendment
July 25, 2000: Chemistry Review #4
August 14, 2000: Amendment
November 6, 2000: Chemistry Review #5
May 17, 2001: Amendment
June 6, 2001: Telephone Deficiency
June 22, 2001: Minor Amendment

10. PHARMACOLOGICAL CATEGORY
H_2 Receptor Antagonist

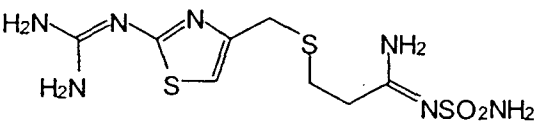
11. Rx or OTC
Rx

12. RELATED ANDA/DMFs
75-610

13. DOSAGE FORM
Tablet

14. POTENCY
20 mg & 40 mg

15. CHEMICAL NAME AND STRUCTURE
Famotidine. $C_8H_{15}N_7O_2S_3$. 337.45. *N*'-(aminosulfonyl)-3-[[[2-[(diaminoethylene)amino]-4-thiazolyl]methyl]thio] Propanimidamide.



16. RECORDS AND REPORTS
N/A

17. COMMENTS
See review

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable

19. REVIEWER
Ijeoma N. Nnamani, Ph.D.

DATE COMPLETED
July 6, 2001

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Chem Review #6

MAR 28 200

38. Chemistry comments to be provided to the applicant

ANDA: 75-611 APPLICANT: **TorPharm**

DRUG PRODUCT: Famotidine Tablets USP, 20 mg and 40 mg

The following deficiencies represent MINOR deficiencies:

1. DMF( ) is deficient and the holder has been informed.

2. Your CoA indicates Famotidine because of the melting point of the drug substance. Please include a quantitative specification of ( ), in your drug substance tests and specifications sheet and resubmit.

3. Revise and resubmit your finished product specifications and stability specifications to reflect your stability data. Your current specifications are high compared to your certificates of Analysis and stability data.

4. We acknowledge the receipt of your updated room temperature data. Please include individual named related compounds 1 to 9, moisture specification, and Q ( )% in your stability report and resubmit.

5. Please submit updated room temperature data, if available.

Sincerely yours,

(/S/)

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research