CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74467

CHEMISTRY REVIEW(S)

Patients at Reduced Dosage After Healing Acute Ulcers, will not be contained in the insert labeling of this ANDA because they expire post July 25, 1997.

BIO ISSUES: ~~**Pending.**~~ Bio found acceptable on Dec. 18, 1995.

ALL INACTIVE INGREDIENTS CITED? **Yes**
OTHER KEY ISSUES:

APPROVAL SUMMARY

CONTAINER LABELS: **1000s (150 mg and 300 mg) - June 8, 1995**

CARTON LABELING (SUBMISSION DATE): None

INSERT LABELING: **November 22, 1995 (Rev. 95-11M)**

FORMULATION/SCORING SUMMARY: **Same as the NDA. Both the 150 mg and 300 mg tablets are NOT scored. The firm revised the shape of the 300 mg tablet to be round.**

COMMENTS OR FUTURE REVISIONS NEEDED: **CONTRAINDICATIONS - Insert (see PRECAUTIONS) at the end of the sentence.**

1° REVIEWER: /S/ 11/29/95

2° REVIEWER:

SUPERVISOR: /S/

DATE: 11/29/95

Division Review Summary

ANDA: 74-467 **DRUG PRODUCT:** Ranitidine Hydrochloride I

FIRM: Geneva Pharmaceutical

DOSAGE FORM: Coated Tablets

STRENGTHS: 150 mg & 300 mg

CGMP STATEMENT/EIR UPDATE STATUS:
Pending results (update submitted 11/16/95).

BIO INFORMATION:
The Division of bioequivalence found the in-vivo studies for Ranitidine Tablet 300 mg strength (lot No. 6493066) in comparison to the innovator's drug product Zantac tablet 300 mg to be incomplete. A Bio deficiency letter was issued on 1/9/95. Pending review of Bio amendment dated 2/24/95.

VALIDATION:
N/A

STABILITY:
Accelerated stability data (40°C and 75% RH) on the smallest (60's) and largest (1,000's) of the container sizes. These data were found to conform to specified limits.

The stability protocol is in conformance with FDA Guidelines. Containers used in the stability studies are the same as those in the container/closure section of the application. The firm wishes to market the finished drug product only in 1,000's. This is reflected in their revised labeling.

LABELING:
Satisfactory, dated 11/28/95.

SIZE OF BIO BATCH:
A batch record for lot No. 6493066, for the 300 mg tablets is appended. A total of tablets were manufactured.

A batch record for lot No. 6493065, for the 150 mg tablets is appended. A total of tablets were manufactured.

DMF # , drug substance manufacturer for Ranitidine Hydrochloride (Form I), was reviewed by E. Ramos and found to be satisfactory, dated July 29, 1995.

SIZE OF STABILITY BATCHES:
Same as the Bio batch.

PROPOSED PRODUCTION BATCH:
a) 150 mg; units.
b) 300 mg; units.

RECOMMENDATION:
Recommend approval of generic drug Ranitidine Hydrochloride Tablets, 150 mg & 300 mg.

CHEMISTRY REVIEWER: **DATE:** December 5, 1995
Edwin Ramos

/S/ 1/2/96

SUPERVISOR:
Ms. Brenda Arnwine

/S/ 1/8/96

ANDA Approval Summary

74-467
ANDA Number

Geneva Pharmaceutical
Applicant Name

Ranitidine Hydrochloride
Established Name of Drug

Tablets
Dosage Form

150 mg & 300 mg
Strength

150 mg--625 cc (1,000's) & 300 mg--1300 cc (1,000's)
Container Size(s)

	Date found Satisfactory	Comment
Labeling	11/28/95	
Chemistry	12/5/95	
GMP's	12/28/95	
Manufacturer-Finished Dosage Form	12/28/95	
Outside Facilities	12/28/95	
Manufacturer(s)-Active Ingredient(s)	12/28/95	

/S/ 1/18/96
Chemist Reviewer — Date

/S/ 1/18/96
Branch Chief — Date

Petition Required ✓ NO ____ YES

Listed Drug Information 505 (j)(2)(A) 3/8/94

Patent Certification 505 (j)(2)(B) 3/8/94

Date Patent/Exclusivity Expires (if applicable)

Patents: 4658 7/25/97; 4731 6/4/02; 4636 5/13/05 (N/A)

Exclusivity: I-120 3/24/98; I-75 5/19/95; D-21 2/25/97; I-116 11/3/97

Bioequivalence Section

Dissolution Required? ____ No ✓ Yes : ____ DB ____ DGD

In vivo study(s) required? ____ No ✓ Yes

300 mg tablet

Study(s) Found Acceptable	12/18/95	300 mg
Waiver Request Granted	12/18/95	150 mg
Total Bioequivalence Requirement Met	12/18/95	

/S/
Administrative Reviewer

1/25/96
Date

Approved _____

Disapproved _____

_____ _____
Director, Division of Chemistry Date

Comments:

1. CHEMIST'S REVIEW NO. 2

2. ANDA # 74-467

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, Colorado 80038-0446

4. LEGAL BASIS for ANDA SUBMISSION
Ranitidine Hydrochloride Tablets, USP, 150 mg and 300 mg are the generic version of the listed drug, **Zantac** 150 mg and 300 mg manufactured by Glaxo. Patent # 4,128,658 which covers Polymorphic Form I will expire on December 5, 1995. Patent #4,521,431 which covers Polymorphic Form II will expire on the year of 2002.

5. SUPPLEMENT
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Ranitidine Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
February 16, 1994-- Original Submission
March 2, 1994-- Telecom Amendment
March 11, 1994-- ANDA New Correspondence
March 21, 1994-- ANDA New Correspondence
November 11, 1994-- ANDA Original Amendment
February 24, 1995-- Bio-New Correspondence

FDA:
February 23, 1994-- Memo by G. Johnston
March 2, 1994-- Telecom Memo by C. Parise
March 8, 1994-- FTR Memo by G. Johnston
March 8, 1994-- Acknowledgement Receipt
March 21, 1994-- Telecom Memo by C. Parise
June 22, 1994-- Deficiency letter
January 9, 1995-- Bio deficiency letter

10. PHARMACOLOGICAL CATEGORY
H2 Receptor Antagonist

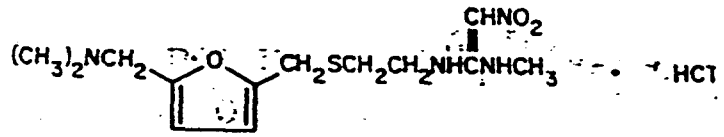
11. Rx or OTC
Rx

12. RELATED DMFs #

13. DOSAGE FORM
Coated Tablets

14. POTENCY
150 mg/300 mg

15. CHEMICAL NAME AND STRUCTURE
N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride.



16. RECORDS AND REPORTS
N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend not approval letter to issue (MAJOR).

19. REVIEWER:
Edwin Ramos

DATE COMPLETED:
February 3, 1995

/S/

3/13/95

(cc Appendix)
3/13/95

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Chem #2

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 74-467

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, Colorado 80038-0446

4. LEGAL BASIS for ANDA SUBMISSION
Ranitidine Hydrochloride Tablets, USP, 150 mg and 300 mg are the generic version of the listed drug, **Zantac** 150 mg and 300 mg manufactured by Glaxo. Patent # 4,128,658 which covers Polymorphic Form I will expire on December 5, 1995. Patent #4,521,431 which covers Polymorphic Form II will expire on the year of 2002.

5. SUPPLEMENT
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Ranitidine Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

February 16, 1994--	Original Submission
March 2, 1994--	Telecom Amendment
March 11, 1994--	ANDA New Correspondence
March 21, 1994--	ANDA New Correspondence
November 11, 1994--	ANDA Original Amendment
February 24, 1995-	Bio-New Correspondence
June 8, 1995--	ANDA Original Amendment

FDA:

February 23, 1994--	Memo by G. Johnston
March 2, 1994--	Telecom Memo by C. Parise
March 8, 1994--	FTR Memo by G. Johnston
March 8, 1994--	Acknowledgement Receipt
March 21, 1994--	Telecom Memo by C. Parise
June 22, 1994--	Deficiency letter
January 9, 1995--	Bio deficiency letter
March 17, 1995--	Deficiency letter

10. PHARMACOLOGICAL CATEGORY
H2 Receptor Antagonist

11. Rx or OTC
Rx

12. RELATED DMFs #

13. DOSAGE FORM
Coated Tablets

14. POTENCY
150 mg/300 mg

15. CHEMICAL NAME AND STRUCTURE
N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride.

16. RECORDS AND REPORTS
N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend not approval letter to issue. Professional Labeling Review was found deficient dated 8/28/95. No chemistry issues are pending.

19. REVIEWER:
Edwin Ramos

DATE COMPLETED:
July 29, 1995

/S/ 10/23/95

/S/ 10/24/95

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Chem #3

1. CHEMIST'S REVIEW NO. 4

2. ANDA # 74-467

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, Colorado 80038-0446

4. LEGAL BASIS for ANDA SUBMISSION
Ranitidine Hydrochloride Tablets, USP, 150 mg and 300 mg are the generic version of the listed drug, **Zantac** 150 mg and 300 mg manufactured by Glaxo. Patent # 4,128,658 which covers Polymorphic Form I will expire on December 5, 1995. Patent #4,521,431 which covers Polymorphic Form II will expire on the year of 2002.

5. SUPPLEMENT
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Ranitidine Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

February 16, 1994--	Original Submission
March 2, 1994--	Telecom Amendment
March 11, 1994--	ANDA New Correspondence
March 21, 1994--	ANDA New Correspondence
November 11, 1994--	ANDA Original Amendment
February 24, 1995-	Bio-New Correspondence
June 8, 1995--	ANDA Original Amendment
October 27, 1995--	New Correspondence-Bio
November 22, 1995--	ANDA Original Amendment
January 22, 1996--	Minor Telecom Amendment

FDA:

February 23, 1994--	Memo by G. Johnston
March 2, 1994--	Telecom Memo by C. Parise
March 8, 1994--	FTR Memo by G. Johnston
March 8, 1994--	Acknowledgement Receipt
March 21, 1994--	Telecom Memo by C. Parise
June 22, 1994--	Deficiency letter
January 9, 1995--	Bio deficiency letter
March 17, 1995--	Deficiency letter
August 28, 1995--	Labeling review
October 27, 1995--	Deficiency letter
January 22, 1996--	Telecom

10. PHARMACOLOGICAL CATEGORY
H2 Receptor Antagonist

11. Rx or OTC
Rx

12. RELATED DMFs #

13. DOSAGE FORM
Coated Tablets

14. POTENCY
150 mg/300 mg

15. CHEMICAL NAME AND STRUCTURE
N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Updated room temperature stability data (24 months) for the 150 mg and 300 mg obtained in the smallest and largest of the marketing containers were provided per our request. All critical assays were found to conform to specifications. However, the organoleptic analysis for the 150 mg tablets shows a slight darkening of the coated tablet at the 24 months test station. The request for a 36 months expiry should consider the organoleptic results.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval letter to issue.

19. REVIEWER:
Edwin Ramos

DATE COMPLETED:
December 5, 1995

/S/ 1/22/96

/S/ 1/22/96

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Chem #4

H2 1

1. CHEMIST'S REVIEW NO. 5

2. ANDA # 74-467

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, Colorado 80038-0446

4. LEGAL BASIS for ANDA SUBMISSION
Ranitidine Hydrochloride Tablets, USP, 150 mg and 300 mg are the generic version of the listed drug, **Zantac** 150 mg and 300 mg manufactured by Glaxo. Patent # 4,128,658 which covers Polymorphic Form I will expire on July, 1997.

5. SUPPLEMENT
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Ranitidine Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

February 16, 1994--	Original Submission
March 2, 1994--	Telecom Amendment
March 11, 1994--	ANDA New Correspondence
March 21, 1994--	ANDA New Correspondence
November 11, 1994--	ANDA Original Amendment
February 24, 1995-	Bio-New Correspondence
June 8, 1995--	ANDA Original Amendment
October 27, 1995--	New Correspondence-Bio
November 22, 1995--	ANDA Original Amendment
January 22, 1996--	Minor Telecom Amendment
January 30, 1996--	Telephone Amendment
March 13, 1997--	Amendment

FDA:

February 23, 1994--	Memo by G. Johnston
March 2, 1994--	Telecom Memo by C. Parise
March 8, 1994--	FTR Memo by G. Johnston
March 8, 1994--	Acknowledgment Receipt
March 21, 1994--	Telecom Memo by C. Parise
June 22, 1994--	Deficiency letter
January 9, 1995--	Bio deficiency letter
March 17, 1995--	Deficiency letter
August 28, 1995--	Labeling review
October 27, 1995--	Deficiency letter
January 22, 1996--	Telecom
January 31, 1996--	TA letter

Edw

10. PHARMACOLOGICAL CATEGORY
H2 Receptor Antagonist

11. Rx or OTC
Rx

12. RELATED DMFs #

13. DOSAGE FORM
Coated Tablets

14. POTENCY
150 mg & 300 mg

15. CHEMICAL NAME AND STRUCTURE
N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
18 and 13 months of room temperature data for the 150 mg and 300 mg, respectively, were submitted to validate the additional container/closure systems. Also, accelerated stability data are included. These data are found to conform to the tentatively approved specifications (attachment 2 & 3, 3/13/97). Packaging specifications are provided. The proposed container/closure systems do not affect the manufacturing equipment, processes and formula. All pertinent information for the additional container closure systems are included (attachment 4).

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval letter to issue. Chemistry review only, no letter will be issued. Awaiting decision from General Counsel.

19. REVIEWER:
Edwin Ramos
/S/

DATE COMPLETED:
April 16, 1997
4/30/97

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Chem # 5

1. CHEMIST'S REVIEW NO. 6

2. ANDA # 74-467

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, Colorado 80038-0446

4. LEGAL BASIS for ANDA SUBMISSION
Patent # 4,128,658 which covers Polymorphic Form I will expire July 25, 1997.

5. SUPPLEMENT
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Ranitidine Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

February 16, 1994--	Original Submission
March 2, 1994--	Telecom Amendment
March 11, 1994--	ANDA New Correspondence
March 21, 1994--	ANDA New Correspondence
November 11, 1994--	ANDA Original Amendment
February 24, 1995-	Bio-New Correspondence
June 8, 1995--	ANDA Original Amendment
October 27, 1995--	New Correspondence-Bio
November 22, 1995--	ANDA Original Amendment
January 22, 1996--	Minor Telecom Amendment
January 30, 1996--	Telephone Amendment
March 13, 1997--	Amendment
April 24, 1997--	Amendment

FDA:

February 23, 1994--	Memo by G. Johnston
March 2, 1994--	Telecom Memo by C. Parise
March 8, 1994--	FTR Memo by G. Johnston
March 8, 1994--	Acknowledgment Receipt
March 21, 1994--	Telecom Memo by C. Parise
June 22, 1994--	Deficiency letter
January 9, 1995--	Bio deficiency letter
March 17, 1995--	Deficiency letter
August 28, 1995--	Labeling review
October 27, 1995--	Deficiency letter
January 22, 1996--	Telecom
January 31, 1996--	TA letter
April 16, 1997--	Chemistry review--acceptable

April 24, 1997-- Labeling review-acceptable
June 1, 1997-- Info letter
July 15, 1997-- Info letter

10. PHARMACOLOGICAL CATEGORY
H2 Receptor Antagonist

11. Rx or OTC
Rx

12. RELATED DMFs #

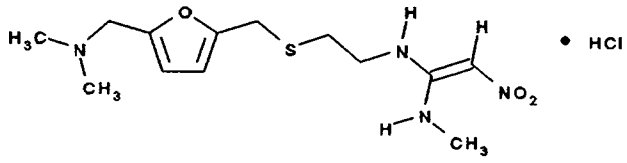
13. DOSAGE FORM
Coated Tablets

14. POTENCY
150 mg & 300 mg

15. CHEMICAL NAME AND STRUCTURE

Ranitidine Hydrochloride USP

$C_{13}H_{22}N_4O_3S.HCl$; M.W. = 350.87



N-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, hydrochloride.
CAS [66357-59-3]

16. RECORDS AND REPORTS
N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval letter to issue.

19. REVIEWER:
Edwin Ramos
/S/

DATE COMPLETED:
August 28, 1997
8/28/97

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Chem # 6