CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74467

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-467 Date of Submission: April 24, 1997

Applicant's Name: Geneva Pharmaceuticals, Inc.

Established Name: Ranitidine Tablets USP, 150 mg and 300 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 150 mg (60s, 100s, 500s, 1000s)
300 mg (30s, 250s, 1000s)
Satisfactorily submitted April 24, 1997.

Professional Package Insert Labeling:
Satisfactorily submitted April 24, 1997.

Revisions needed post-approval: The following exclusivities -
I-116 (11/3/97) - Maintenance of Healing of Erosive Esophagitis
I-120 (3/29/98) - Maintenance Therapy for Gastric Ulcer Patients at Reduced Dosage After Healing Acute Ulcers

Container Labels - Asterisk Strength on Main Display Panel and Each tablet" Statement on

BASIS OF APPROVAL: Item Submitted - clarify Strength "as Hydrochloride"

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Zantac®

NDA Number: 18-703

NDA Drug Name: Zantac® (Ranitidine Tablets USP)

NDA Firm: Glaxo Wellcome

Date of Approval of NDA Insert and supplement #: 11/27/96 (S-055)

Has this been verified by the MIS system for the NDA? No (system down)

Was this approval based upon an OGD labeling guidance? Yes

If yes, give date of labeling guidance: February 1997

Basis of Approval for the Container Labels: Side-by-sides submitted

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book? O BOOK - RANITIDINE HCL	X		
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Labeling(continued)	Yes	No	N.A.
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. Has "very soluble in water" as does the L.G.-RLD has "soluble in water"		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. MODEL LABELING - Labeling Guidance revised 2/97 based on approved RLD labeling for Zantac; Glaxo Wellcome, Inc., Revised December 1995; Approved November 27, 1996.

2. Geneva's product is made with Form I ranitidine.

3. The patent for Form I ranitidine expires 7/25/97. The remaining exclusivities are as follows:

   I-116 (11/3/97) - Maintenance of Healing of Erosive Esophagitis

   I-120 (3/29/98) - Maintenance Therapy For Gastric Ulcer Patients At Reduced Dosage After Healing Acute Ulcers

4. The 150 mg tablet container labels have "150 mg" in white print in a black box while the 300 mg tablet has "300 mg" in black print in a white box.

5. Storage/dispensing:

   USP: Preserve in a tight, light-resistant container. No temperature recommendations.

   ANDA: Store at CRT. Store in a dry place, and protect from light. Dispense in a tight, light-resistant container.

   NDA: Store between 15^{0}-30^{0}C (59^{0}-86^{0}F) in a dry place. Protect from light. Replace cap securely after each opening.

6. SCORING:

   Both strengths for both the NDA and the ANDA are unscored.

7. Components/composition:

   All components are listed in the DESCRIPTION section. The list can be found in attachment #2 in the 3/11/94 correspondence in Vol. 1.1.

8. Containers: (CRC info from chemist review # 5)

   ANDA: 150 mg - 60s (CRC), 100s, 500s, 1000s
   300 mg - 30s (CRC), 250s, 1000s

   NDA: 150 mg - 60s, 180s, 500s, 1000s and unit dose of 100
   300 mg - 30s, 250s and unit dose of 100

9. The tablet descriptions are accurate as portrayed in the HOW SUPPLIED section per chemist review # 5.

10. Bio approval sign-off January 31, 1996.

Date of Review: 5/15/97 **Date of Submission: April 24, 1997**

Primary Reviewer: Adolph Vezza **Date:** 5/16/97

/S/

Team Leader: John Grace **Date:** 5/30/97

/S/

cc:

ANDA 74-467
DUP/DIVISION FILE
HFD-613/AVezza for DKonigstein/JGrace (no cc)
njg/5/16/97¦X:\NEW\FIRMSAM\GENEVA\LTRS&REV\74467.APL
Review

RECORD OF TELEPHONE CONVERSATION

re: New FPL insert labeling needed and need labeling with 3-13-97 amendment for new container closures

I phoned Beth Brannan to communicate a request for new FPL needed before full approval later in the year.

I advised her of changes briefly and stated I would like to fax a copy of our revised guidance which incorporates everything. Further, I would enclose the highlights and directions in a separate cover note.

I also took this opportunity to remind her that two further exclusivities will expire post-approval. The insert should be revised with each exclusivity expiration. A supplement should be forwarded perhaps 30-60 days prior to each expiration. I recommended they not order large quantities, as well.

She expressed she liked the Office's new quick notification process and appreciated the reminder of the exclusivities and tip not to order a lot.

Typically, she said, with a TA, the final minor amendment is submitted ~90 days shy of full approval date, which is 4-25-97 in this case. Do I want a separate labeling amendment? I replied that was up to her.

I also intended to mention the 3-13-97 amendment - they added additional container/closure sizes but this amendment did not contain any labeling. I called her back and left a voice-mail message stating container labels should be submitted and that the HOW SUPPLIED section should be revised to reflect the added container sizes. - if they submit to correct them.

DATE 4-3-97

ANDA NUMBER
74-467

PRODUCT NAME

Ranitidine Tablets

FIRM NAME -
Geneva

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Beth Brannan

TELEPHONE NUMBER

303-466-2400

SIGNATURE

/S/

David Konigstein,
Labeling Reviewer

4-3-97

X:\NEW\FIRMSAM\GENEVA\TELECONS\74467.01L

I noted while glancing through the [illegible] a couple of times

ANDA 74-467 Geneva Pharmaceuticals, Inc.

Ranitidine Tablets USP, 150 mg and 300 mg

Upon further review of this drug product's insert labeling and due to changes in the approved package insert labeling of the reference listed drug, Zantac® (Glaxo Wellcome, Inc.; Approved 11-27-96; Revised December 1995), we have revised our labeling guidance (Revised 2/97).

Briefly, the highlights of the revisions are the following:

1. "Ranitidine" rather than should be used throughout the text, except in the DESCRIPTION section.

2. DESCRIPTION - Chemical name shored up per USP 23 monograph. Note italics, hyphens, and capitals. There should be no spaces.

3. CLINICAL PHARMACOLOGY

   Clinical Trials

   a. Active Duodenal Ulcer, last paragraph - Delete the last sentence

   b. Gastroesophageal Reflux Disease (GERD) - Additional text added as a new last paragraph. ("In two additional ... severity of heartburn.")

4. INDICATIONS AND USAGE

   Item 5. Treatment of GERD - Revise to read "... occurs within 24 hours after starting ..." ["24 hours" rather than "1 or 2 weeks"].

Please revise your insert labeling to be in accordance with the accompanying revised labeling guidance. Submit 12 copies of final printed insert labeling as an amendment to your tentatively approved application. The amendment should be designated as a "MINOR AMENDMENT" in your cover letter.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last insert, with all differences annotated and explained.

If you have any questions or concerns regarding this labeling matter, please contact David Konigstein, Labeling Reviewer, at 301-594-0365.

RECORD OF TELEPHONE CONVERSATION

Ann Bryant called and asked if we could fax a copy of the most recently approved labeling for ranitidine. I said no and that she would have to go through FOI. She said she needed it quicker than FOI could get it to her. I said I could not. She requested to speak to Jerry Phillips. She did and he told her the same thing. Then she called back again on 11/9/95 wanting to know why we requested changes in her FPL labeling. I explained the GATT extension affected one of the exclusivities and would now need to be put into the labeling. She said ok.

DATE
11/8/95

ANDA NUMBER
74-467

IND NUMBER

TELECON

INITIATED BY
X **APPLICANT/ SPONSOR**

FDA

MADE
_X **BY TELE.**

_ **IN PERSON**

PRODUCT NAME
Ranitidine Tablets

FIRM NAME
Geneva

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Ann Bryant

TELEPHONE NUMBER
(303) 438-4292

SIGNATURE
/S/

Geneva Pharmaceuticals, Inc. Reviewer: F. Nouravarsani
Ranitidine HCl Tablets
300 mg
ANDA #74-467
Submission Date:
February 24, 1995

FILE

Beth Brannan, Director
Drug Regulatory Affairs
Phone: (303) 466-2400

1. Reports of the statistical data analysis, GLM Procedure, including 26 subjects was not submitted.

2. The firm was requested to submit a table including **all** original values together with reassayed, values which were used in the study, reason for reassaying, and rationale for the values used. The firm did not submit all of the original values.

9/13/95
Sd/ B...

10-11-95 !
Sue PANOSIAN:
was called and the above DATA
was requested
10-11-95

LABELING REVIEW WORKSHEET

FIRM: **Geneva Pharmaceuticals, Inc.** ANDA: **74-467**
DRUG: **Ranitidine Tablets USP, 150 mg and 300 mg**

LABELING OF THE LISTED DRUG

FIRM: Glaxo Pharmaceuticals and the Labeling Guidance for Ranitidine Tablets USP, Rev. 11/93 NDA# 18-703
APPROVAL DATE: March 29, 1995 REV.DATE: March 1995

CONTAINER LABELS

APPROVED COPY ON FILE? **No**
USP CONTAINER/CLOSURE REQUIREMENTS: **Preserve in a tight, light-resistant container. No temperature recommendations.**
RECOMMENDED STORAGE STATEMENT:
ANDA: **Store at CRT. Store in a dry place, and protect from light. Dispense in a tight, light-resistant container.**
NDA: **Store between 15°-30°C (59°-86°F) in a dry place. Protect from light. Replace cap securely after each opening.**
OTHER KEY ISSUES: **The June 8, 1995 submission contains container labels for the 1000s container size. In the previous submission the firm had submitted container labels for package sizes of 30's, 100's and 500's (150 mg) and 30's, 250's (300 mg). The firm stated the 1000s are the only package size they intend to distribute. (See page 6 in June 8, 1995 Amendment)**

INSERT LABELING

PATENT & EXCLUSIVITY ISSUES: a. The patent for Form I, patent (4128658), expires on July 25, 1997 (This has been extended by GATT from December 5, 1995). Due to this extension the insert labeling ~~needs to~~ has to be updated to include the indication for Alternative Dosage of 300 mg once daily after the evening meal . Form II, patent (4521431), expires on June 4, 2002.

b. Patent # 5028432 is a patent for the gelatin capsule formulation entitled Pharmaceutical capsules containing ranitidine . This patent expires on July 2, 2008. Patent 4880636 expires on May 13, 2008. Patent 4585790 expires May 11, 2004 (extended by GATT from 4/29/2003) and patent 5102665 expires June 23, 2009 (extended by GATT from 4/7/2009).

c. Exclusivity for I-75 (Treatment of Endoscopically Diagnosed Erosive Esophagitis) expires on May 19, 1995.

d. Exclusivity for D-21 (Alternative Dosage of 300 mg once daily after the evening meal) expires on February 28, 1997.

e. Exclusivity for I-116 (Maintenance of Healing of Erosive Esophagitis) expires on November 3, 1997.

f. Because the exclusivity for Form 1 expires on July 25, 1997, the indication for Alternative Dosage of 300 mg daily after the evening meal will now be included in the labeling. The indications for Maintenance of Healing of Erosive Esophagitis and Maintenance Therapy for Gastric Ulcer

EXCLUSIVITY STATEMENT

According to information published in the list of Approved Drug Products 17th Ed.,

Supplement 4, Zantac® Tablets are entitled to a period of mardeting exclusivity for:

I-116	Maintenance of healing of erosive Esophagitis	Expires: November 3, 1997
I-120	Maintenance and therapy for gastric ulcer patients at reduced dosage after healing acute ulcers	Expires: March 29, 1998

GENEVA PHARMACEUTICALS, INC

Beth Brannan, Director
Drug Regulatory Affairs

8/29/97
Date

CERTIFICATION OF SUBMISSION OF FIELD COPY

In accordance with 21 CFR 314.96(b) (September 8, 1993 **Federal Register** Final Rule Notice), Geneva Pharmaceuticals, Inc. hereby certifies that a field copy of required information from our amendment to our Abbreviated New Drug Application for Ranitidine Tablets, USP, 150 mg and 300 mg has been provided to the Denver District office, FDA.

In addition, we hereby certify that the field copy of this amendment is a true copy of the submission to the Office of Generic Drugs.

Beth Brannan

11/22/95

Beth Brannan Date

Director

Drug Regulatory Affairs

REVIEW OF PROFESSIONAL LABELING #3

Orig. Amendment (Major)

FPL - Container labels and Package Insert labeling

DATE OF REVIEW: August 28, 1995

ANDA #: 74-467

NAME OF FIRM: Geneva Pharmaceuticals, Inc.

NAME OF DRUG: Ranitidine Tablets USP, 150 mg and 300 mg

DATE OF SUBMISSION: June 8, 1995

COMMENTS:

CONTAINER: 1000s (150 mg and 300 mg)

Satisfactory. We acknowledge the change in package size.

INSERT:

1. GENERAL COMMENT

   Due to GATT patent extensions your insert labeling should be revised as indicated below. In addition, you should amend your application as appropriate.

2. CLINICAL PHARMACOLOGY

   Clinical Trials, *Erosive Esophagitis* - Revise the subsubsection heading to appear italicized and not in bold print.

3. INDICATIONS AND USAGE

   Revise the sixth indication to read as follows:

   Treatment of endoscopically diagnosed erosive esophagitis. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with ranitidine 150 mg qid.

4. ADVERSE REACTIONS

   Integumentary - Revise to read:

   ...cases of erythema multiforme, and rarely, alopecia.

5. DOSAGE AND ADMINISTRATION

a. Active Duodenal Ulcer - Revise paragraph 1 to read:

...daily. An alternative dosage of 300 mg once daily after the evening meal or at bedtime can be used for patients in whom...

b. Maintenance Therapy - Revise this subsection heading to read:

Maintenance of Healing of Duodenal Ulcers

6. HOW SUPPLIED

We encourage you to list the NDC numbers in this section.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their package insert labeling, then prepare and submit final printed insert labeling. Please note that final printed insert labeling is not required for tentative approval of an application if it is granted with more than 90 days remaining from the date when full approval can be considered. We will accept final "printers proof" for the insert only. Should further information become available relating to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

NOTE TO THE CHEMIST:

1. Please note that the firm has changed their package sizes as follows: Accelerated stab is ...

a) 150 mg (1000's) rather than (30's, 100's and 500's 60's).

b) 300 mg (1000's), rather than (250's and 1000's).

2. The firm has changed the shape of the 300 mg tablet from a "modified capsule" to a "round tablet". Is this acceptable?

Q "Comparative Dissolution Profi... submitted dated 6/7/95. Acce... 8/95

FOR THE RECORD:

1. This review was based on the labeling guidance for Ranitidine Tablets USP (Revised November 1993) and new labeling of the listed drug Zantac® (Glaxo; Approved March 29, 1995; Revised March 1995).

2. The firm has submitted a second ranitidine application which is titled Form II (ANDA 74-232), this application is Form I. Form I is a granular substance that is soluble in water. Form II is a crystalline substance that is very soluble in water. (See Description section).

3. Patents/Exclusivity:

   a. The patent for Form I, patent (4128658), expires on July 25, 1997 (This has been extended by GATT from December 5, 1995). Due to this extension the insert labeling needs to be updated to include the indication for "Alternative Dosage of 300 mg once daily after the evening meal". Form II, patent (4521431), expires on June 4, 2002.

   b. Patent # 5028432 is a patent for the gelatin capsule formulation entitled "Pharmaceutical capsules containing ranitidine". This patent expires on July 2, 2008. Patent 4880636 expires on May 13, 2008. Patent 4585790 expires May 11, 2004 (extended by GATT from 4/29/2003) and patent 5102665 expires June 23, 2009 (extended by GATT from 4/7/2009).

   c. Exclusivity for I-75 (Treatment of Endoscopically Diagnosed Erosive Esophagitis) expired on May 19, 1995.

   d. Exclusivity for D-21 (Alternative Dosage of 300 mg once daily after the evening meal) expires on February 28, 1997.

   e. Exclusivity for I-116 (Maintenance of Healing of Erosive Esophagitis) expires on November 3, 1997.

   f. Because the exclusivity for Form 1 expires on July 25, 1997, the indication for Alternative Dosage of 300 mg daily after the evening meal will now be included in the labeling. The indications for Maintenance of Healing of Erosive Esophagitis and Maintenance Therapy for Gastric Ulcer 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.

4. Storage and Dispensing:

USP: Preserve in a tight, light-resistant container. No temperature recommendations.

NDA: Store between 15°-30° (59°-86°F) in a dry place. Protect from light. Replace cap securely after each opening.

ANDA: Store at CRT 15°-30°C (59°-86°F). Store in a dry place, and protect from light. Dispense in a tight, light-resistant container.

5. Scoring:

NDA: Both strengths unscored.

ANDA: Both strengths unscored.

6. Components/Composition:

All components are listed in the DESCRIPTION section. The list can be found in attachment #2 in the 3/11/94 correspondence in Vol. 1.1.

7. The firm states that they intend to market a container of 1000 only. See page 6 of response from firm in the June 8, 1995 amendment. See NOTE TO THE CHEMIST.

8. The established name should read "Ranitidine Tablets USP" rather than "Ranitidine Hydrochloride Tablets". The USP uses Ranitidine Hydrochloride as the compound and Ranitidine Tablets as the finished dosage form. This differs from the innovator's title.

9. The firm has revised the shape of the 300 mg tablet from a "modified capsule" to a "round tablet". See response from firm on page 7 in the June 8, 1995 amendment. See NOTE TO CHEMIST.

Carol Zimmermann

/S/ 9/15/95

cc: ANDA 74-467
HFD-613/CZimmermann/AVezza/CHoppes (no cc)
caz 8/28/95
74467JUN.95

/S/ 9/15/95

REVIEW OF PROFESSIONAL LABELING #2

Orig. Amendment (Major)

DRAFT - Package insert labeling and FPL - Container labels

DATE OF REVIEW: February 7, 1995

ANDA #: 74-467 NAME OF FIRM: Geneva Pharmaceuticals, Inc.

NAME OF DRUG: Ranitidine Tablets USP, 150 mg and 300 mg

DATE OF SUBMISSION: November 11, 1994

COMMENTS:

CONTAINER: 30's, 100's, 500's (150 mg) and 30's, 250's (300 mg)

Satisfactory. We acknowledge the change in package sizes.

INSERT:

1. GENERAL COMMENT

   Please increase the readability of the text in your insert. It is difficult to read in some areas.

2. PRECAUTIONS

   Pediatric Use - Revise as follows:

   ...in pediatric patients have...

3. ADVERSE REACTIONS

   Integumentary - Revise as follows:

   ...cases of erythema...

4. OVERDOSAGE

   Paragraph 3, line 1 - Revise so that "mg/kg" appear on the same line.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their package insert labeling, then prepare and submit final printed insert labeling. Please note that final printed insert labeling is not

required for tentative approval of an application if it is granted with more than 90 days remaining from the date when full approval can be considered. We will accept final "printers proof" for the insert only. Should further information become available relating to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

NOTE TO THE CHEMIST:

1. The firm has stated in their communication dated November 11, 1994, that they will comply with the Poison Prevention Packaging Act regarding child-resistant closures. However, the data submitted contains a 60 unit fill bottle and no 30 unit fill bottle. The company is not planning to manufacture a 60 tablet container. Will this data be adequate to ensure a CRC closure on the 30's package size?

   The subject issue will be conveyed to the applicant. More data is needed. E. Ramos 3/1/95

2. Please note that the Firm has changed their package sizes as follows:

   a) 150 mg (30's, 100's, 500's) rather than (60's and 1000's claimed as previously

   b) 300 mg (250's rather than the 1000's), the 30's were retained.

FOR THE RECORD:

1. This review was based on the labeling guidance for Ranitidine Tablets USP (Revised November 1993) and new labeling of the listed drug Zantac® (Glaxo; Approved November 10, 1994; Revised September 1994).

2. The firm has submitted a second ranitidine application which is titled Form II (ANDA 74-232), this application is Form I. Form I is a granular substance that is soluble in water. Form II is a crystalline substance that is very soluble in water. (See Description section).

3. Patents/Exclusivity:

   a. The patent for Form I, patent (4128658), expires on December 5, 1995. Form II, patent (4521431), expires on June 4, 2002.

b. Patent # 5028432 is a patent for the gelatin capsule formulation entitled "Pharmaceutical capsules containing ranitidine". This patent expires on July 2, 2008.

c. Exclusivity for I-75 (Treatment of Endoscopically Diagnosed Erosive Esophagitis) expires on May 19, 1995.

d. Exclusivity for D-21 (Alternative Dosage of 300 mg once daily after the evening meal) expires on February 28, 1997.

e. Exclusivity for the indication of Healing Erosive Esophagitis approved on November 3, 1994, will get exclusivity until 11/3/97. See E-Mail dated 2/16/95, from Mary Ann Holovac.

f. Because the exclusivity for Form 1 expires in 1995, the indication for Alternative Dosage of 300 mg daily after the evening meal and Healing Erosive Esophagitis, which both expire in 1997, will not be contained in the insert labeling of this ANDA.

4. Storage and Dispensing:

USP: Preserve in a tight, light-resistant container. No temperature recommendations.

NDA: Store between 15°-30° (59°-86°F) in a dry place. Protect from light. Replace cap securely after each opening.

ANDA: Store at CRT 15°-30°C (59°-86°F). Store in a dry place, and protect from light. Dispense in a tight, light-resistant container.

5. Scoring:

NDA: Both strengths unscored.

ANDA: Both strengths unscored.

6. Components/Composition:

All components are listed in the DESCRIPTION section. The list can be found in attachment #2 in the 3/11/94 correspondence in Vol. 1.1.

7. The firm states that they will package the 30 size bottle in a CRC cap. See NOTE TO THE CHEMIST #1

8. The established name should read "Ranitidine Tablets USP" rather than "Ranitidine Hydrochloride Tablets". The USP uses Ranitidine Hydrochloride as the compound and Ranitidine Tablets as the finish dosage form. This differs from the innovators title.

Carol Zimmermann

cc: ANDA 74-467
HFD-613/CZimmermann\APayne\JPhillips (no cc)
mpd/2/23/95; (95) 74467NOV.94
Review
final

/S/ 2/24/95

/S/ 2/24/95

RECORD OF TELEPHONE CONVERSATION

Ranitidine Tablets 74-467

Jennifer Hutchinson of Geneva phoned and asked me to check the information they submitted for their Paragraph IV certification to see if the letter from Geneva notifying Glaxo of their intentions. She indicated that the submission was dated March 11, 1994.

I requested the ANDA from the document room and looked at the referenced submission. It did not contain the notification to Glaxo.

I phoned Jennifer Hutichinson and informed her that the infomation was not with the submission.

She Indicated that she would send an amendment to include this information.

DATE
March 21, 1994

ANDA NUMBER
74-467

IND NUMBER

TELECON

INITIATED BY MADE

X **APPLICANT/**
X **BY SPONSOR**
TELE.

FDA _ **IN PERSON**

PRODUCT NAME
Ranitidine Tablets 150 mg and 300 mg

FIRM NAME
Geneva

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Jennifer Hutchinson

TELEPHONE NUMBER
303-466-2400

SIGNATURE
Cecelia M. Parise

/S/

REVIEW OF PROFESSIONAL LABELING #1

ANDA

DRAFT

DATE OF REVIEW: May 23, 1994

ANDA 74-467

NAME OF FIRM: Geneva Pharmaceuticals, Inc.

NAME OF DRUG: Ranitidine Tablets USP, 150 mg and 300 mg

DATE OF SUBMISSION: February 16, 1994

COMMENTS:

Container:

1. Please assure the prominence of the product name and strength.

2. Capitalize the "P" and "I" that appears in the company name on the main panel.

3. The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). Your proposed container of 30 (300 mg) and 60 (150 mg) appear to be in this category. We believe that these packages should comply with the Act. Please comment.

4. Please differentiate between your two product strengths by the use of boxing, contrast colors, or some other means.

Insert:

1. GENERAL COMMENT

   Please be consistent with where you begin the text following a section heading.

2. DESCRIPTION

   a. Paragraph 1, Line 3 - "hydrochloride" rather than

3. CLINICAL PHARMACOLOGY

a. Pharmacokinetics

i. Paragraph 2 - "(150 mmol)" rather than

ii. Paragraph 4, Line 6 - "ranitidine intravenously" rather than

iii. Clinical Trials

(1). Maintenance Therapy in Duodenal Ulcer (Table 3) - Revise the fourth column to read: No. of Patients.

(2). Gastric Ulcer

Paragraph 2 - "...ranitidine hydrochloride...".

(3). Gastroesophageal...

(a) Paragraph 1, Line 3 - ....ranitidine 150 mg bid was more...

(b) Paragraph 2, Line 1 - "...ranitidine 150 mg bid..."

(c) Paragraph 2, Line 2 - "...1 to 2 weeks..." rather than

(d) Delete the last paragraph.

(e) Add the following paragraph and table as the final subsection:

Erosive Esophagitis: In two multicenter, double-blind, randomized, placebo-controlled, 12-week trials performed in the United States, ranitidine 150 mg qid was significantly more effective than placebo in healing endoscopically-diagnosed erosive esophagitis and in relieving

associated heartburn. The erosive esophagitis healing rates were as follows:

EROSIVE ESOPHAGITIS PATIENT HEALING RATES

	Healed/Evaluable	
	Placebo*	Ranitidine HCL 150 mg qid*
	n=229	n=215
Week 4	43/198 (22%)	96/206 (47%)
Week 8	63/176 (36%)	142/200 (71%)
Week 12	92/159 (58%)	162/192 (84%)

*All patients were permitted p.r.n. antacids for relief of pain.
+p< 0.001 versus placebo.

No additional benefit in healing of esophagitis or in relief of heartburn was seen with a ranitidine dose of 300 mg qid.

4. INDICATIONS AND USAGE

a. Item 5 - Revise as follows:

...starting therapy with rantidine 150 mg bid. (Delete the second sentence).

b. Add the following as item 6:

Treatment of endoscopically-diagnosed erosive esophagitis. Healing of endoscopically-diagnosed erosive esophagitis occurs at 4 weeks (47%), 8 weeks (71%), and 12 weeks (84%) of therapy with ranitidine 150 mg qid. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with ranitidine.

c. Revise the last paragraph to read as follows:

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; GERD; and erosive esophagitis.

5. CONTRAINDICATIONS

Revise as follows:

Ranitidine is contraindicated in patients... drug or any of the ingredients...

6. PRECAUTIONS

a. Add the following as item 3 of the General subsection:

Rare reports suggest that ranitidine may precipitate acute porphyric attacks in patients with acute porphyria. Ranitidine should therefore be avoided in patients with a history of acute porphyria.

b. Drug Interactions

The third sentence should begin the second paragraph.

c. Your subsection headings should be of the same prominence as seen in your other sections.

7. ADVERSE REACTIONS

a. Hepatic, line 3 - "intravenously" rather than (appears twice).

b. Musculoskeletal - "...arthralgias and myalgias."

8. DOSAGE AND ADMINISTRATION

Insert the following below the GERD subsection.

Erosive Esophagitis: The current recommended adult oral dosage is 150 mg four times a day.

9. HOW SUPPLIED

a. Line 1, - Ranitidine Tablets USP, for oral...

b. Please indicate that the tablets are unscored.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their container labels and package insert labeling, then prepare and submit final printed container labels and draft insert labeling.

NOTE TO THE CHEMIST:

Please confirm whether the 30 and 60 tablets package size have CRC. If the answer is yes, I will delete comment 43 under container.

43 per A Payne Worklist 6/13/94

FOR THE RECORD

1. Review based on the labeling guidance(Revised Nov. 1993) for the listed drug (Zantac; Glaxo; Approved April 5, 1993; Revised July 1992).

2. It appears that the firm has submitted a second ranitidine application which is titled Form I (ANDA 74-467) which differs from another application Form II (ANDA 74-232). Form I is a granular substance that is soluble in water. Form two is a crystalline substance that is very soluble in water. (See DESCRIPTION section).

3. Exclusivity for I-75 (Treatment Of Endoscopically Diagnosed Erosive Esophagitis expires on May 19, 1995).

4. Patent (4128658) expires Dec.05, 1995 for form I.

5. Storage/Dispensing

   ANDA: CRT, store in a dry place and protect from light. Replace cap securely after each opening.
   Dispense in a tight, light-resistant container.

   NDA: Store between 15°-30°C (59°- 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

   USP: Preserve in tight, light-resistant containers.

6. Neither the NDA nor ANDA products are scored.

Angela Payne

MEMO TO THE RECORD

The firm currently has an application on file for Ranitidine Hydrochloride Tablets. The pending application utilizes Type II ranitidine HCl. Type II ranitidine has patent protection until June 4, 2002. The proposed application (74-467) uses Type I ranitidine HCl as the NDS. The firm has submitted a paragraph IV certification with this ANDA.

A meeting was held on March 7, 1994, to discuss the acceptability of two ANDAs for the same drug product held by a single applicant. Dr. Guyer, Florence Fang, Cecelia Parise, Don Hare, Shari Sheehan, Justina Molzon, Bob Pollock, and Gordon Johnston were in attendance.

The regulations do not permit an applicant to file a second application for the same drug product if it already the subject of an **approved** application. In this case, Geneva's ANDA utilizing Type II ranitidine is unapproved. The proposed ANDA (Type I ranitidine) requires manufacturing procedures and controls that are substantially different from those used in the manufacture of the Type II product. Because of these differences in manufacturing and controls, the information would not be permitted in a single application. Thus, based on the above issues it was determined that an application would be filed for Type I ranitidine.

/S/ 3/8/94

Gordon Johnston

CERTIFICATION OF SUBMISSION OF FIELD COPY

In accordance with 21 CFR 314.96(b) (September 8, 1993 Federal Register Final Rule Notice), Geneva Pharmaceuticals, Inc. hereby certifies that a field copy of required information for the ANDA 74-467 Ranitidine Tablets USP, 150 mg and 300 mg amendment has been provided to the Denver district office.

In addition, we hereby certify that the field copy of this amendment is a true copy of the technical section described in 21 CFR 314.94(a)(9).

Beth Brannan 3/2/94

Beth Brannan Date

Director

Drug Regulatory Affairs

RECORD OF TELEPHONE CONVERSATION

I contacted Jennifer Hutchinson at Geneva to ask that they revise the second paragraph on the third copy certification. The word amendment was inserted in place of application.

In addition, I requested that they send one more copy of the draft labeling. The application contained three copies instead of four.

DATE
March 2, 1994

ANDA NUMBER
74-467

IND NUMBER

TELECON

INITIATED BY	MADE
_ APPLICANT/ SPONSOR	X BY TELE.
X FDA	_ IN PERSON

PRODUCT NAME
Ranitidine Tablets, 150 mg and 300 mg

FIRM NAME
Geneva

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Jennifer Hutchinson Regulatory Affairs

TELEPHONE NUMBER
303-466-2400

SIGNATURE
Cecelia M. Parise

/S/

File: 74-467

M E M O R A N D U M

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

DATE : February 23, 1994

TO : Director
Division of Bioequivalence (HFD-650) /S/

FROM : Chief, Regulatory Support Staff
Office of Generic Drugs (HFD-632) 2/24/94

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Ranitidine Tablets USP, 150 mg and 300 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355(4)(B)(iv).

Geneva Pharmaceuticals, Inc. has submitted an ANDA for Ranitidine Tablets. The ANDA contains a certification pursuant to 21 USC 355(j)(2)(A)(vii)(iv) stating that a patent expiring June 4, 2002, will not be infringed by the manufacture or sale of the proposed product. In order to accept an ANDA for filing that contains such a patent certification, the Agency must formally make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the study submitted by Geneva Pharmaceuticals, Inc. on February 16, 1994, for its Ranitidine product satisfies the statutory requirements of "completeness" so that the ANDA may be filed and that a period of six months of market exclusivity can be granted to the applicant who submitted the first substantially complete ANDA under 21 USC 355(j)(4)(B)(iv).

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

✓ Study meets statutory requirements

_____ Study does **NOT** meet statutory requirements

Reason:

/S/ 2/25/94

Director, Division of Bioequivalence Date