CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-655

CORRESPONDENCE

ANDA 74-655

OCT 30 1997

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
Broomfield, CO 80038-0446

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 31, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ranitidine Capsules, 150 mg and 300 mg (present as the hydrochloride).

Reference is also made to our approval letter dated October 22, 1997.

This letter addresses issues related to the 180-day exclusivity provisions under section 505(j)(4)(B)(iv) of the Act.

The listed drug product referenced in your application is subject to periods of patent protection which expire on June 4, 2002, (patent 4,521,431) and February 22, 2010 (patent 5,028,432). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of ranitidine hydrochloride will not infringe on the patent or that the patent is otherwise invalid. You further informed the Agency that Glaxo, Inc. initiated a patent infringement suit against you in the United States District Court for the District of New Jersey (Glaxo Wellcome Inc., Glaxo Group Limited and Allen and Hanbury's Limited v. Novartis Corporation, Geneva Pharmaceuticals Inc., Interchem Trading Corporation, and Union Quimico Farmaceutica S.A., Civil Action No. 94-1921, 94-4589 and 96-3849). You also have notified the Agency, that on October 1, 1997, the District Court hearing the patent case issued a Stipulated Dismissal pursuant to Rule 41(a)(1)(ii). This order states:

> [T]he Dismissal will have the full force and effect of a decision of non-infringement of United States Patent Nos. 4,521,431, 4,128,658, 4,672,133 from which no appeal can be taken; and pursuant to 21 USC 355(j)(4)(B)(iii), the thirty (30) month stay of approval of Geneva Pharmaceutical Inc.'s ANDA 74-655 is dissolved and the Food and Drug Administration may approve ANDA 74-655 immediately.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

The Division of Bioequivalence has determined your Ranitidine Capsules, 150 mg(base) and 300 mg(base), to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zantac GELdose Capsules, 150 mg(base) and 300 mg(base), respectively, of Glaxo Wellcome, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

2/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Geneva pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400

FEDERAL EXPRESS

OCT 0 1 1997

MINOR AMENDMENT

Douglas Sporn
Office Of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, Maryland 20855

NDA ORIG AMENDMENT
N/AM

RECEIVED

OCT 0 2 1997

GENERIC DRUGS

RE: ANDA 74-655 Ranitidine Capsules, 150 mg and 300 mg (Form I)
Minor Amendment - Request for Full Approval

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting a minor amendment to our tentatively approved Abbreviated New Drug Application for Ranitidine Capsules, 150mg and 300mg (Form I) in accordance with Section 505(j) of the Food, Drug and Cosmetic Act and with 21 CFR Part 314.96(a).

Reference is made to your communication dated July 24, 1997 and Geneva's minor amendment dated August 29, 1997.

1. Per Section 505(j)(4)(B)(iii) and your communication dated July 24, 1997, Geneva hereby request full approval of ANDA 74-655 Ranitidine Capsules, 150mg and 300mg due to a settlement agreement reached between Geneva Pharmaceuticals, Inc. and Glaxo Wellcome, Inc and Glaxo Group Limited, October 1, 1997.

2. The ranitidine capsules litigation with Glaxo involving Glaxo's alleged claims of patent infringement (Civil Action Nos. 94-1921, 94-4589 and 96-3849 (NHP) (Consolidated) has been dismissed with prejudice. Attached to this letter is a copy of the Stipulated Dismissal of the cases which has been signed by the parties and entered by the Court.

As indicated in the Stipulated Dismissal, the Court has ordered, and the parties have agreed, that "this Dismissal will have the full force and effect of a decision of non-infringement of United States Patent Nos. 4,521,431; 4,128,658; and 4,672,133 from which no appeal can be taken; and pursuant to 21 U.S.C. 355(j)(4)(B)(iii), the thirty (30) month stay of approval of Geneva Pharmaceuticals Inc.'s ANDA 74-655 is dissolved and the Food and Drug Administration may approve 74-655 immediately."

3. Per a phone conversation between Julia Johnson (Labeling Reviewer, OGD) and Archie Phillips (Geneva) August 26, 1997, a final review of our proposed labeling was conducted by Ms. Johnson and it was determined that there were no outstanding issues,

changes to innovator labeling or expired exclusivity indications that needed to be added to our labeling since the date of the tentative approval.

4. Geneva's Minor Amendment dated August 29,1997 details updates regarding the replacement of USP 23, Method I, Organic Volatile Impurities (OVI's) with in-house Raw Material Method RM-1789 to control the five USP listed OVIs and the process solvents used by the raw material manufacturer. The amendment also proposes batch size decreases to both the 150mg and 300mg strengths due to changes in our marketing forecast.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,
GENEVA PHARMACEUTICALS, INC.

Beth Brannan

Beth Brannan, Director
Drug Regulatory Affairs

BB:ap
Attachment

Geneva pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

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FEDERAL EXPRESS

MINOR AMENDMENT

AUG 29 1997

NDA GRIG AMENDMENT

N/A M

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 74-655 Ranitidine Capsules 150 mg and 300 mg (Form I)
Minor Amendment - Chemistry and Manufacturing Controls:
Analytical & Batch Size Decrease

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting a minor amendment to our tentatively approved Abbreviated New Drug Application for Ranitidine Capsules, 150 mg and 300 mg (Form I), in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR Part 314.70(c)(1).

Geneva has replaced USP 23, Method I Organic Volatile Impurities (OVI's) with Raw Material Method control the five USP listed OVIs and the process solvents used by the manufacturer. USP 23 Method I was not selective for . USP 23 Method I procedure allows for a validated column with different packing to be used when the chromatography contains volatile impurities with comparable retention times.

Differences between USP and Method RM-1789 are:

Parameter	USP
Column Packing	Dimethylpolysiloxane
Oven Program	35°C hold for 5min to 175°C @ 8°C/min to 260° @ 35°C/min hold for 16 min
Detector Temperature	260°
Inj.Port Temperature	70°C
Standard Preparation	Five USP OVIs
Sample Preparation	20 mg/mL Concentration

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GENERIC DRUGS

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The Raw Material Specification Sheet has been updated to include each individual USP OVI and acetone, ethanol, and ethylacetate with their individual specifications.

The revised Raw Material Specification Sheet and Raw Material Method are provided in Attachment 1.

The raw material manufacturer's specifications are provided in Attachment 2.

Additionally, Geneva would like to propose batch size decreases to the 150 mg and 300 mg strengths due to changes in the marketing forecast.

The table below represents the proposed batch size decreases:

150 mg		300 mg	
Current	**Proposed**	**Current**	**Proposed**

Note: Please note that the proposed decrease for the 300 mg batch size returns it to it's original ANDA batch size of

Revised Master Manufacturing Forms for both the 150 mg and 300 mg strengths are provided in Attachment 3.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed envelope provided.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

BB/ap
Enclosures

Geneva pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400

FEDERAL EXPRESS

July 10, 1997

AMENDMENT

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

NEW CORRESP
NC

RE: ANDA 74-655 Ranitidine Capsules (I), 150 mg and 300 mg
Amendment - Patent and Exclusivity Information

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for ANDA 74-655 Ranitidine Capsules (I), 150 mg and 300 mg in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96 (a).

Reference is made to calls between Beth Brannan (Geneva) and Peter Rickman (FDA) on 4/17/97 and 7/7/97, and a call between Archie Phillips (Geneva) and Cassandra Sherrod (FDA) on 6/13/97. Also please reference Geneva's telephone amendment submitted 6/13/97.

There are three patents listed in the Approved Drug Products 17th Ed. for Ranitidine Capsules (Zantac®):

- Patent # 4,128, 658 will expire on 7/25/97. Geneva submitted a Paragraph III Certification for this patent in our original ANDA submission on 3/31/95.

- Patent # 4,521,431 will expire on 6/4/2002. Geneva submitted a paragraph IV Certification for this patent on 6/25/96. Concurrent with that submission Geneva notified Glaxo per 21 CFR 314.95(a) and 314.95(c) (Please refer to pages 8-14 in our 6/25/96 submission. In attachment 1 we are providing a receipt for certified mail along with a copy of the Return Receipt signed at Glaxo. Geneva was sued by Glaxo on 8/16/96 Civil Action No. 96-3849 NHP regarding this certification..

RECEIVED

GENERIC DRUGS

GP097

- Patent # 5,028,432 will expire on 2/22/2010. Geneva submitted a Paragraph IV Certification for this patent in our original ANDA submitted 3/31/95. Notification to the patent holder (Glaxo Wellcome) was sent on 5/31/95. A copy of the Patent Certification Notice, the certified mail receipt, and the Return Receipt signed by Glaxo are provided in Attachment 2. Geneva was not sued by Glaxo in regards to that certification.

Provided in Attachment 3 is an exclusivity statement for I-120 expiring 3/28/98.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

Enclosures

BB/slc

Geneva pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

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FEDERAL EXPRESS

TELEPHONE AMENDMENT

Douglas Sporn
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

June 27, 1997

RE: ANDA 74-655 Ranitidine Hydrochloride Capsules, 150 mg and 300 mg
Amendment - Chemistry, Manufacturing Controls: Finished Product Dissolution Specifications

Dear Director:

We are submitting an amendment to our unapproved Abbreviated New Drug Application for Ranitidine Hydrochloride Capsules, in accord with Section 505(j) of the Federal Food, Drug and Cosmetic Act and with 21 CFR Part 314.96(a).

Reference is made to your communication dated January 29, 1997 from the Division of Bioequivalence and the telephone conversation on June 25, 1997 between Edwin Ramos (OGD Chemistry Reviewer) and Beth Brannan (Geneva).

Geneva commits to incorporating the following dissolution testing into the stability and quality control programs:

900 mL H_2O, 37 °C
Apparatus 2 (paddles) @ 50 rpm

In addition, we have updated our stability protocols to add a related compound specification for other individual impurities. This update was necessary because we inadvertently failed to make the revision in our January 16,1997 Minor Amendment.

The following revised documents are provided in support of the change in dissolution specifications: a) Finished Product Specification and Method in Attachment 1, and b) Stability Protocols in Attachment 2.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan

Beth Brannan, Director
Drug Regulatory Affairs
BB:ap
Enclosures

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JUL 0 1997
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Geneva pharmaceuticals, inc.

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(303) 466-2400

FEDERAL EXPRESS

June 13, 1997

TELEPHONE AMENDMENT

NEW CORRESP
NC

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 74-655 Ranitidine Capsules, 150 mg and 300 mg
(Form I) Telephone Amendment - Patent: Notification of Legal Action

Dear Sir:

Geneva Pharmaceuticals, Inc. is hereby submitting a Telephone Amendment to our unapproved Abbreviated New Drug Application for Ranitidine Capsules, 150 mg and 300 mg (Form I) in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act and with 21 CFR Part 314.96.

Reference is made to the telephone conversation between Casandra Sherrod, (OGD) and Archie Phillips (Geneva) on June 13, 1997.

Per CFR 314.107(f)(2) the following information and certification are provided:

NOTIFICATION OF LEGAL ACTION

- ANDA Number: 74-655
- Abbreviated New Drug Name: Ranitidine Capsules 150 mg and 300 mg
- Established Drug Product Name: Ranitidine Capsules
- Geneva certifies that it is subject to a lawsuit filed by Glaxo Wellcome Inc., Glaxo Group Limited, and Allen & Hansburys Limited, Civil Action Number 96-3849 (NHP) in the United States District Court for the District of New Jersey August 16, 1996 for infringement of Patents 4,521,431 and 4,562,133. This action was filed within the 45 day time clock.

Geneva certifies that the content requirements for notification of the patent owner under CFR 314.95(b) and (c) were met.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

C. Fitzsimons for

Beth Brannan, Director
Drug Regulatory Affairs

RECEIVED
JUN 18 1997
GENERIC DRUGS

GP097

Geneva pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446
(303) 466-2400 • FAX (303) 438-4600

FEDERAL EXPRESS

MINOR AMENDMENT

March 25, 1997

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

RE: ANDA 74-655 Ranitidine Capsules, 150 mg and 300 mg (Form I)
Minor Amendment - Labeling

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for Ranitidine Capsules, 150 mg and 300 mg (Form I) in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96 (a).

Reference is made to your facsimile communication dated March 14, 1997. Response to your comments is provided in the order of appearance in this communication.

1. Container - 500s

   Container labels for both the 150 mg and 300 mg strengths have been revised as requested.

2. Insert

   The general comment is acknowledged.
   All requested revisions have been made.

Final printed container labeling and insert labeling are provided in Attachment 1.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

RECEIVED
MAR 2 6 1997
GENERIC DRUGS

Enclosures
BB/kak

Geneva pharmaceuticals, inc.

2555 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400 • FAX (303) 466-3717

FEDERAL EXPRESS

MINOR AMENDMENT

Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North, Room 150
7500 Standish Place
Rockville, Maryland 20855

January 16, 1997

ORIG AMENDMENT
N/AM

RE: ANDA 74-655 Ranitidine Capsules, 150 mg and 300 mg (Form I)
Minor Amendment - Chemistry, Labeling and Manufacturing Controls

Dear Director:

We are submitting an amendment to our Abbreviated New Drug Application for Ranitidine Hydrochloride Capsules, 150 mg and 300 mg (Form I) in accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act and CFR Part 314.96(a).

Reference is made to your written communication of August 14, 1996. Response to your comments is provided in the order of appearance in your communication.

A. Chemistry Deficiencies

Page(s) 3

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

1/16/97

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

BB/ap
Enclosures as indicated

ORIGINAL

Geneva pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400

FEDERAL EXPRESS

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JUL 12 1996

GENERIC DRUGS

Director,
Office of Generic Drugs,
Division of Bioequivalence - HFD-650
Centre for Drug Evaluation and Research,
Metro Park North 2,
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 74-655 Ranitidine Hydrochloride Capsules, 150 mg and 300 mg
Amendment - Bioequivalence Study

Dear Director:

We are submitting an amendment to our unapproved Abbreviated New Drug Application for Ranitidine Hydrochloride Capsules, in accord with Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to your written communications of January 22, 1996 and May 10, 1996.

We acknowledge that our April 16, 1996 amendment failed to address all concerns expressed in the January 22, 1996 communication.

1. The long-term stability of ranitidine in plasma for 83 days is provided in Table S1.1 of Attachment 1.

   Comparison samples were stored at -20 °C overnight because sample extraction for the stability evaluation was scheduled for the next day. The time required for sample preparation, extraction, and injection makes it difficult for this procedure to be completed in one working day. Please note that it was demonstrated that the spiked samples were stable when stored overnight at -20 °C.

2. A table indicating the approximate run duration in minutes is provided in Attachment 1. This table indicates that the duration of injection for samples analysed on curves CTE12, CTE14, CTE17, CTE18 and CTE 31 in some cases exceeded the substantiated autosampler stability period of 2.8 h. Additional autosampler stability has been established for a period of 4.4 h and the data are provided in Attachment 1. Note however, that, the present autosampler stability procedure does not require a QC at the lower limit of quantitation. Since QC and standard samples are extracted individually (*i.e.* not pooled) there is always sample to sample variability. Thus, the mean of the QC values is considered to be most representative of the nominal value in which percent deviations are generated (refer to SOP AL-G-1521-04 in Attachment 2). This will

not alter the trend that may exist in the stability data, but will provide a more reliable "reference" to calculate the percent deviation compared to a single sample.

3. The equation representing the calculation of "percent difference" in tables S6 and S7 of the analytical report was inadvertently incorrect. However, the formula actually used in the program to calculate the percent difference between the stability and comparison samples was correct. The amended equation (*i.e.* tables S6 and S7) is provided in Attachment 1.

4. The procedure of extraction of ranitidine in human plasma, outlined in [redacted] "A [redacted] for the Determination of Ranitidine in Human Plasma" was conducted by [redacted] In most cases, samples coded "lost in processing" were the result of a high content of insoluble material present in the plasma samples. This caused the [redacted] on cartridges to become blocked resulting in low or zero volume of eluate. In all cases, samples originally deemed "lost in processing" were reanalysed and the final concentration values are presented in the T3 tables of the analytical report.

5. [redacted], "Analytical Method Validation" is provided in Attachment 2.

6. Comparative 12 unit dissolution data on both the test and reference products in 900 mL water at 37 °C, using both USP apparatus 2 (paddles) at 50 rpm and apparatus 1 (baskets) at 100 rpm at the suggested sampling times of 10, 20, 30 and 45 min are provided in Attachment 3. Since the reference product for both the 150 mg and 300 mg strengths had expired, unexpired lots were also tested under these dissolution conditions per the telephone conversation between Jason Gross of FDA and Sue Panesar of Geneva on February 1, 1996.

7. The waiver of bioequivalence study requirements for the 150 mg strength is provided in Attachment 4. Also included are the formula compositions for the 150 mg and 300 mg strengths.

This information is provided for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan

Beth Brannan, Director
Drug Regulatory Affairs

bb/skp

Enclosures

Geneva pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400

FEDERAL EXPRESS

June 25, 1996

Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2 Room 150
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 74-655 Ranitidine Capsules, 150 mg and 300 mg
Amendment - Patent Certification

Dear Director:

We are submitting an amendment to our unapproved Abbreviated New Drug Application for Ranitidine Capsules, 150 mg and 300 mg in accord with Section 505(j) of the Federal Food, Drug and Cosmetic Act.

A revised patent certification for Ranitidine patent No. 4,521,431 is being submitted.

This information is submitted toward the approval of ANDA 74-655.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed, stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan

Beth Brannan, Director
Drug Regulatory Affairs

BB:cs
Enclosures

Geneva pharmaceuticals, inc.

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FEDERAL EXPRESS

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NEW CORRES BIOAVAILABILITY mod 7
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APR 17 1996
GENERIC DRUGS

Director,
Office of Generic Drugs,
Division of Bioequivalence - HFD-650
Centre for Drug Evaluation and Research,
Metro Park North 2,
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 74-655 Ranitidine Hydrochloride Capsules, 150 mg and 300 mg
Amendment - Bioequivalence Study

Dear Director:

We are submitting an amendment to our unapproved Abbreviated New Drug Application for Ranitidine Hydrochloride Capsules, in accord with Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to your written communication of January 22, 1996.

1. The long-term stability of ranitidine in plasma for the 70 day required period will be completed April 22, 1996. The revised stability data will be submitted once it is available.

   Comparison samples were stored at -20 °C overnight because sample extraction for the stability evaluation was scheduled for the next day. The time required for sample preparation, extraction, and injection makes it difficult for this procedure to be completed in one working day. Please note that it was demonstrated that the spiked samples were stable when stored overnight at -20 °C.

2. A table indicating the approximate run duration in minutes is provided in Attachment 1. This table indicates that the duration of injection for samples analysed on curves CTE12, CTE14, CTE17, CTE18 and CTE 31 in some cases exceeded the substantiated autosampler stability period of 2.8 h. Additional autosampler stability has been established for a period of 4.4 h and the data are provided in Attachment 1. Note however, that, the present autosampler stability procedure does not require a QC at the lower limit of quantitation. Since QC and standard samples are extracted individually (*i.e.* not pooled) there is always sample to sample variability. Thus, the mean of the QC values is considered to be most representative of the nominal value in which percent deviations are generated (refer to SOP AL-G-1521-04 in Attachment 2). This will not alter the trend that may exist in the stability data, but will provide a more reliable "reference" to calculate the percent deviation compared to a single sample.

3. The equation representing the calculation of "percent difference" in tables S6 and S7 of the analytical report was inadvertently incorrect. However, the formula actually used in the program to calculate the percent difference between the stability and comparison samples was correct. The amended equation (*i.e.* tables S6 and S7) is provided in Attachment 1.

4. The procedure of extraction of ranitidine in human plasma, outlined in SOP GC-M-2352-00, "A 1 for the Determination of Ranitidine in Human Plasma" was conducted by . most cases, samples coded "lost in processing" were the result of a high content of insoluble material present in the plasma samples. This caused the cartridges to become blocked resulting in low or zero volume of eluate. In all cases, samples originally deemed "lost in processing" were reanalysed and the final concentration values are presented in the T3 tables of the analytical report.

5. "Analytical Method Validation" is provided in Attachment 2.

6. Comparative 12 unit dissolution data on both the test and reference products in 900 mL water at 37 °C, using both USP apparatus 2 (paddles) at 50 rpm and apparatus 2 (baskets) at 100 rpm at the suggested sampling times of 10, 20, 30 and 45 min is provided in Attachment 3. Since the reference product for both the 150 mg and 300 mg strengths had expired, unexpired lots were also tested under these dissolution conditions per the telephone conversation between Jason Gross of FDA and Sue Panesar of Geneva on February 1, 1996.

7. The waiver of bioequivalence study requirements for the 150 mg strength is provided in Attachment 4. Also included are the formula compositions for the 150 mg and 300 mg strengths.

This information is provided for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

bb/skp

Enclosures

ANDA 74-655

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, Colorado 80038-0446

AUG 14 1996

Dear Ms. Brannan:

This is in reference to your abbreviated new drug application dated March 31, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ranitidine Capsules, 150 mg and 300 mg.

Reference is also made to your amendment dated February 5, 1996.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. Please provide a detailed description of the

(i.e., 1050-1040cm^{-1}) to obtain more sensitivity. Please provide FT-IR data to support or refute our request.

B. Labeling Deficiencies

1. GENERAL COMMENT

Due to GATT patent extensions the DOSAGE AND ADMINISTRATION section of your insert labeling should be revised as indicated below. In addition, you should amend your application as appropriate.

2. CONTAINER: 30's, 60's, 90's and 500's

Satisfactory in final print.

3. INSERT

a. After further review we request that you revise to read "ranitidine" rather than "ranitidine hydrochloride" throughout the text of the insert except in the DESCRIPTION section.

b. INDICATIONS AND USAGE

Revise indication number six to read as follows:

...ranitidine 150 mg q.i.d.

[NOTE: "150 mg" rather than "50 mg"]

c. DOSAGE AND ADMINISTRATION

Active Duodenal Ulcer - Revise the second sentence of paragraph one to read as follows:

...daily after the evening meal or at bedtime...

Please revise your insert labeling, as instructed above, and submit final printed labeling. 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 submission with all differences annotated and explained. Please note that we

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

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 8/14/96.

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Geneva pharmaceuticals, inc.

2655 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400 • FAX (303) 466-3717

MAJOR AMENDMENT

FEDERAL EXPRESS

NDA ORIG AMENDMENT FPL

N/A 2

Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2 Room 150
7500 Standish Place
Rockville, Maryland 20855

February 5, 1996

RECEIVED

FEB 0 6 1996

GENERIC DRUGS

RE: ANDA 74-655 Ranitidine Capsules, 150 mg and 300 mg
Major Amendment - Chemistry, Labeling, Manufacturing and Controls

We are submitting an amendment to our unapproved Abbreviated New Drug Application for Ranitidine Capsules, 150 mg and 300 mg in accordance with Section 505 (j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to your communications dated September 21, 1995 which stated our response would be characterized as a major amendment.

A. Chemistry Deficiencies

Page(s) 1

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

2/6/96

B. Labeling Deficiencies

Reference is made to item B, #'s 1-4 and #'s 1-6 of your communication concerning container and insert labeling.

The Container labeling has been revised as requested.

Additionally, insert labeling has been revised. All requested revisions have been made with one exception. At this time, we have chosen not to include NDC numbers in the How Supplied section. This decision has been made so that we may maintain consistency throughout our Product line. This exemption is provided for in 21CFR Part 201.2.

Final printed container labeling and draft insert labeling is provided in Attachment 5.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

BB/ap

Enclosures as indicated

ANDA 74-655

Geneva Pharmaceuticals, Inc.
Attention: Ms. Beth Brannan
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, Colorado 80020-0446

SEP 21 1995

Dear Ms. Brannan:

This is in reference to your abbreviated new drug application dated March 31, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ranitidine Capsules, 150 mg and 300 mg.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

B. Labeling Deficiencies

CONTAINER: 30's, 60's, 90's and 500's

1. Increase the prominence of the established name and strength.

2. Revise the "Each tablet contains" statement to read as follows:

   Each capsule contains ranitidine hydrochloride equivalent to ...mg of ranitidine.

3. Storage recommendations - "Store" rather than "Sore".

4. Net quantity; revise to read:

   XXX capsules (rather than "tablets")

INSERT:

1. GENERAL COMMENT

   All subsection headings should be consistent throughout the text of the insert. Please revise so that your subsection headings have the same prominence and typeset.

2. CLINICAL PHARMACOLOGY

   Clinical Trials - Add "hydrochloride" in the following places:

a. Gastroesophageal Reflux Disease

i. Paragraph 1, line 3 - ...hydrochloride 150 mg bid...

ii. Paragraph 2, line 1 - ...hydrochloride 150 mg bid...

b. Erosive Esophagitis

a. Line 2 - ...hydrochloride 150 mg qid...

b. Table, last column - Place the "+" symbol next to the percentages listed in this column.

3. INDICATIONS AND USAGE

a. Ranitidine capsules are indicated in...

b. Indication #5 - ...ranitidine hydrochloride...

c. Revise indication #6 to read:

...esophagitis. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with ranitidine hydrochloride 150 mg qid.

4. PRECAUTIONS

Revise the "Pediatric Use" subsection to read as follows:

...in pediatric patients have...

5. OVERDOSAGE

Paragraph 2 - Place "229 mg/kg per day" on the [illegible] line.

6. DOSAGE AND ADMINISTRATION

Active Duodenal Ulcer - Delete "hydrochloride" from the second line of the first paragraph.

HOW SUPPLIED

a. You have indicated that the 150 mg capsule will be imprinted with GG 615 and the 300 mg capsule will be imprinted with GG 614. However, your master formula indicates that the 150 mg capsule will be imprinted with GG 614 and the 300 mg with GG 615. Please revise accordingly.

b. We encourage the inclusion of your NDC numbers.

Please revise your container labels and package insert labeling, then prepare and submit final printed container labels and draft package insert labeling.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 9/20/95

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Geneva pharmaceuticals, inc.

2555 W. Midway Blvd. • P.O. Box 446 • Broomfield, CO 80038-0446

(303) 466-2400 • FAX (303) 466-3717

FEDERAL EXPRESS

March 31, 1995

Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

RE: Ranitidine Capsules, 150 mg and 300 mg

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting an Abbreviated New Drug Application for Ranitidine Capsules, 150 mg and 300 mg as required by Section 505 of the Federal Food, Drug, and Cosmetic Act, and described in 21 CFR 314.94.

A comprehensive table of contents is provided which shows the volume and page number of our submission's contents, as required by the regulations part 314.94(a)(1).

The blue archival copy (3 volumes) contains the complete application. Additionally, the blue archival copy contains an analytical specifications and methods packet. Triplicate copies of raw material and finished product specifications and in-house methods have been placed in a plastic sleeve located just inside the cover.

The red review copy (3 volumes) contains labeling and the technical portion of our application. The orange review copy (3 volumes) contains bioequivalence information. A bioequivalence study has been completed comparing Geneva's Ranitidine Capsules, 150 mg and 300 mg to Zantac®/Gel Dose™ Capsules, 150 mg and 300 mg. A full copy of the study and requests for waiver for the 150 mg strength products are provided.

This information is submitted for your review and approval.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

GENEVA PHARMACEUTICALS, INC.

Beth Brannan, Director
Drug Regulatory Affairs

Enclosures as Indicated.