CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74823

Trade Name Terazosin Hydrochloride Capsules 1mg, 2mg, 5mg and 10mg

Generic Name Terazosin Hydrochloride Capsules

Sponsor Geneva Pharmaceuticals, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74823

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74823

APPROVAL LETTER

ANDA 74-823

MAR 30 1998

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2655 W. Midway Boulevard
P.O. Box 446
Broomfield, CO 80038-0446

Dear Madam:

Reference is made to your abbreviated new drug application dated December 29, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Terazosin Hydrochloride Capsules, 1 mg(base), 2 mg(base), 5 mg(base) and 10 mg(base).

Reference is also made to your amendments dated February 16 and April 29, 1996; December 12, 1997; and January 28, February 23, March 3, March 12, and March 19, 1998.

The listed drug product referenced in your application is subject to periods of patent protection which expire on February 17, 2000 (Patent No. 4,251,532 [the '532 patent]), June 29, 2010 (Patent No. 5,212,176 [the '176 patent]), and April 29, 2013 (Patents No. 5,294,615 [the '615 patent], 5,412,095 [the '095 patent], and 5,504,207 [the '207 patent]). Your application contains patent certifications under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use or sale of Terazosin Hydrochloride Capsules will not infringe on the patents and that the patents are otherwise invalid. Section 505(j)(4)(B)(iii) of the Act provides that " . . . approval shall be made effective immediately unless an action is brought for infringement of a patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received." You have informed the Agency that Geneva Pharmaceuticals, Inc. has complied with the requirements of Section 505(j)(2)(B) of the Act. You have also informed the Agency that the NDA and patent holder, Abbott Laboratories, initiated a patent infringement suit pertaining only to the '615 patent against you in the United States District Court for the Northern District of Illinois (Eastern Division) (Civil Action No. 96-C-1762). You have also notified the Agency that the above action against Geneva Pharmaceuticals, Inc. was dismissed by the plaintiff, Abbott Laboratories, without prejudice.

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 labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Terazosin Hydrochloride Capsules, 1 mg(base), 2 mg(base), 5 mg(base), and 10 mg(base) to be bioequivalent and, therefore therapeutically equivalent to the listed drug (Hytrin Capsules 1 mg(base), 2 mg(base), 5 mg(base), and 10 mg(base), respectively, of Abbott Laboratories. 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,

3/30/94

Roger L. Williams, M.D.
Deputy Center Director
for Pharmaceutical Science
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74823

FINAL PRINTED LABELING

ANDA SUBMISSION

TERAZOSIN HYDROCHLORIDE CAPSULES
7204-2
PATIENT INFORMATION

30 1998

PATIENT INFORMATION
ABOUT

TERAZOSIN HYDROCHLORIDE

When used to treat HYPERTENSION or
BENIGN PROSTATIC HYPERPLASIA (BPH)

Please read this leaflet before you start taking terazosin hydrochloride. Also, read it each time you get a new prescription. This is a summary and should NOT take the place of a full discussion with your doctor who has additional information about terazosin hydrochloride. You and your doctor should discuss terazosin hydrochloride and your condition before you start taking it and at your regular checkups.

Terazosin hydrochloride is used to treat high blood pressure (hypertension). Terazosin hydrochloride is also used to treat benign prostatic hyperplasia (BPH) in men. This leaflet describes terazosin hydrochloride as a treatment for hypertension or BPH.

What is hypertension (high blood pressure)?

Blood pressure is the tension of the blood within the blood vessels. If blood is pumped too forcefully, or if the blood vessels are too narrow, the pressure of the blood against the walls of the vessels rises.

If high blood pressure is not treated, over time, the increased pressure can damage blood vessels or it can cause the heart to work too hard and may decrease the flow of blood to the heart, brain, and kidneys. As a result, these organs may become damaged and not function correctly. If high blood pressure is controlled, this damage is less likely to happen.

Treatment options for hypertension

Non-drug treatments are sometimes effective in controlling mild hypertension. The most important lifestyle changes to lower blood pressure are to lose weight, reduce salt, fat, and alcohol in the diet, quit smoking, and exercise regularly. However, many hypertensive patients require one or more ongoing medications to control their blood pressure. There are different kinds of medications used to treat hypertension. Your doctor has prescribed terazosin hydrochloride for you.

What terazosin hydrochloride does to treat hypertension

Terazosin hydrochloride works by relaxing blood vessels so that blood passes through them more easily. This helps to lower blood pressure.

What is BPH?

The prostate is a gland located below the bladder of men. It surrounds the urethra (you-REETH-rah), which is a tube that drains urine from the bladder. BPH is an enlargement of the prostate gland. The symptoms of BPH, however, can be caused by an increase in the tightness of muscles in the prostate. If the muscles inside the prostate tighten, they can squeeze the urethra and slow the flow of urine. This can lead to symptoms such as:

- a weak or interrupted stream when urinating
- a feeling that you cannot empty your bladder completely
- a feeling of delay when you start to urinate
- a need to urinate often, especially at night, or
- a feeling that you must urinate right away.

Treatment options for BPH

There are three main treatment options for BPH:

- Program of monitoring or "Watchful Waiting". Some men have an enlarged prostate gland, but no symptoms, or symptoms that are not bothersome. If this applies, you and your doctor may decide on a program of monitoring including regular checkups, instead of medication or surgery.
- Medication. There are different kinds of medication used to treat BPH. Your doctor has prescribed terazosin hydrochloride for you. See "What terazosin hydrochloride does to treat BPH" below.
- Surgery. Some patients may need surgery. Your doctor can describe several different surgical procedures to treat BPH. Which procedure is best depends on your symptoms and medical condition.

What terazosin hydrochloride does to treat BPH

Terazosin hydrochloride relaxes the tightness of a certain type of muscle in the prostate and at the opening of the bladder. This may increase the rate of urine flow and/or decrease the symptoms you are having.

- Terazosin hydrochloride helps relieve the symptoms of BPH. It does NOT change the size of the prostate, which may continue to grow. However, a larger prostate does not necessarily cause more or worse symptoms.
- If terazosin hydrochloride is helping you, you should notice an effect on your particular symptoms in 2 to 4 weeks of starting to take the medication.
- Even though you take terazosin hydrochloride and it may help you, terazosin hydrochloride may not prevent the need for surgery in the future.

Other important facts about terazosin hydrochloride for BPH

- You should see an effect on your symptoms in 2 to 4 weeks. So, you will need to continue seeing your doctor to check your progress regarding your BPH and to monitor your blood pressure in addition to your other regular checkups.
- Your doctor has prescribed terazosin hydrochloride for your BPH and not for prostate cancer. However, a man can have BPH and prostate cancer at the same time. Doctors usually recommend that men be checked for prostate cancer once a year when they turn 50 (or 40 if a family member has had prostate cancer). These checks should continue even if you are taking terazosin hydrochloride. Terazosin hydrochloride is not a treatment for prostate cancer.
- About Prostate Specific Antigen (PSA). Your doctor may have done a blood test called PSA. Your doctor is aware that terazosin hydrochloride does not affect PSA levels. You may want to ask your doctor more about this if you have had a PSA test done.

What you should know while taking terazosin hydrochloride for hypertension or BPH

WARNINGS

Terazosin Hydrochloride Can Cause a Sudden Drop in Blood Pressure After the VERY FIRST DOSE. You may feel dizzy, faint, or "light-headed" particularly after you get up from bed or from a chair. This is more likely to occur after you've taken the first few doses, but can occur at any time while you are taking the drug. It can also occur if you stop taking the drug and then re-start treatment.

Because of this effect, your doctor may have told you to take terazosin hydrochloride at bedtime. If you take terazosin hydrochloride at bedtime but need to get up from bed to go to the bathroom, get up slowly and cautiously until you are sure how the medicine affects you. It is also

(See Reverse)

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(See Reverse)

important to get up slowly from a chair or bed at any time until you learn how you react to terazosin hydrochloride. You should not drive or do any hazardous tasks until you are used to the effects of the medication. If you begin to feel dizzy, sit or lie down until you feel better.

- You will start with a 1 mg dose of terazosin hydrochloride. The dose will be increased as your body gets used to the effect of the medication.
- Other side effects you could have while taking terazosin hydrochloride include drowsiness, blurred or hazy vision, nausea, or "puffiness" of the feet or hands. Discuss any unexpected effects you notice with your doctor.

Extremely rarely, terazosin and similar medications have caused painful erection of the penis, sustained for hours and unrelieved by sexual intercourse or masturbation. This condition is serious, and if untreated it can be followed by permanent inability to have an erection. If you have a prolonged abnormal erection, call your doctor or go to an emergency room as soon as possible.

How to take terazosin hydrochloride

Follow your doctor's instructions about how to take terazosin hydrochloride. You must take it every day at the dose prescribed. Talk with your doctor if you don't take it for a few days, you may have to restart it at a 1 mg dose and be cautious about possible dizziness. Do not share terazosin hydrochloride with anyone else; it was prescribed only for you.

Keep terazosin hydrochloride and all medicines out of the reach of children.

Store at controlled room temperature between 15°-30°C (59°-86°F). Protect from light and moisture.

FOR MORE INFORMATION ABOUT TERAZOSIN HYDROCHLORIDE AND HYPERTENSION OR BPH, TALK WITH YOUR DOCTOR, NURSE, PHARMACIST OR OTHER HEALTH CARE PROVIDER.

Rev. 97-12M C97/12
7204-2

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

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Rev. 97-12M C97/12
7204-2

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

2.

Terazosin Hydrochloride Capsules

10 mg*

CAUTION: Federal law prohibits dispensing without prescription.

100 CAPSULES

Geneva pharmaceuticals, inc.

N 3 0781-2054-01 7

*Each capsule contains:
Terazosin hydrochloride equivalent to 10 mg terazosin.
Usual Dosage: See package insert.
Store at controlled room temperature between 15°-30°C (59°-86°F). Protect from light and moisture. Dispense in a tight, light-resistant container. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
Rev. 97-12M C97/12
Manufactured By
Geneva Pharmaceuticals, Inc., Broomfield, CO 80020

LOT:

EXP.:

APPROVED

MAR 30 1998

Terazosin Hydrochloride Capsules

10 mg*

CAUTION: Federal law prohibits dispensing without prescription.

500 CAPSULES

Geneva pharmaceuticals, inc.

N 3 0781-2054-05 5

APPROVED

*Each capsule contains:
Terazosin hydrochloride equivalent to 10 mg terazosin.
Usual Dosage: See package insert.
Store at controlled room temperature between 15°-30°C (59°-86°F).
Protect from light and moisture.
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KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Rev. 97-12M C97/12
Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP.:

MAR 30 1998

Terazosin Hydrochloride Capsules

5 mg*

CAUTION: Federal law prohibits dispensing without prescription

100 CAPSULES

Geneva pharmaceuticals, Inc.

N 3 0781-2053-01 0

*Each capsule contains:
Terazosin hydrochloride equivalent to 5 mg terazosin.
Usual Dosage: See package insert.
Store at controlled room temperature between 15°-30°C (59°-86°F). Protect from light and moisture. Dispense in a tight, light-resistant container. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
Rev. 97-12M Manufactured By C97/12
Geneva Pharmaceuticals, Inc., Broomfield, CO 80020

LOT:

EXP:

APPROVED

MAR 30 1998

Terazosin Hydrochloride Capsules

5 mg*

CAUTION: Federal law prohibits dispensing without prescription

500 CAPSULES

Geneva pharmaceuticals, Inc.

N 3 0781-2053-05 8

APPROVED

*Each capsule contains:
Terazosin hydrochloride equivalent to 5 mg terazosin.
Usual Dosage: See package insert.
Store at controlled room temperature between 15°-30°C (59°-86°F).
Protect from light and moisture.
Dispense in a tight, light-resistant container.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Rev. 97-12M C97/12

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP.:

MAR 30 1998

N 3 0781-2052-01 3

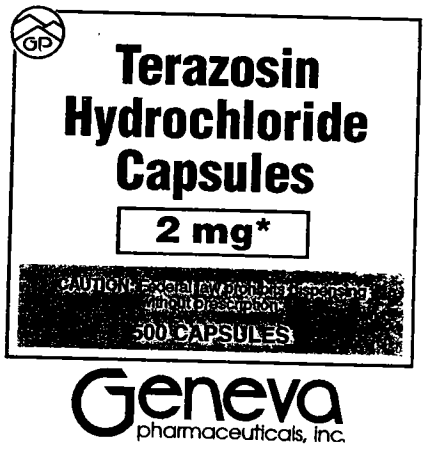
*Each capsule contains:
Terazosin hydrochloride equivalent to 2 mg terazosin.
Usual Dosage: See package insert.
Store at controlled room temperature between 15°-30°C (59°-86°F). Protect from light and moisture. Dispense in a tight, light-resistant container. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
Rev. 97-12M C97/12
Manufactured By
Geneva Pharmaceuticals, Inc., Broomfield, CO 80020

LOT:

EXP.:

APPROVED

JAN 30 1998



N 3 0781-2052-05 1

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*Each capsule contains:
Terazosin hydrochloride equivalent to 2 mg terazosin.
Usual Dosage: See package insert.
Store at controlled room temperature between 15°-30°C (59°-86°F).
Protect from light and moisture.
Dispense in a tight, light-resistant container.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Rev. 97-12M C97/12

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP.:

JAN 30 1998

MARGO

Terazosin Hydrochloride Capsules

1 mg*

CAUTION: Federal law prohibits dispensing without prescription.

100 CAPSULES

Geneva pharmaceuticals, inc.

N 3 0781-2051-01 6

*Each capsule contains:
Terazosin hydrochloride equivalent to 1 mg terazosin.
Usual Dosage: See package insert.
Store at controlled room temperature between 15°-30°C (59°-86°F). Protect from light and moisture. Dispense in a tight, light-resistant container. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**
Rev. 97-12M C97/12
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1 mg*

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500 CAPSULES

Geneva pharmaceuticals, inc.

N 3 0781-2051-05 4

APPROVED

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Protect from light and moisture.
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MAR 30 1998

LOT:

EXP.:

4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74823

CHEMISTRY REVIEW(S)

Office of Generic Drugs

Chemistry, Manufacturing and Control Review

1. **CHEMISTRY REVIEW** Addendum #1 to CR #4

2. **ANDA #** 74-823

3. **NAME AND ADDRESS OF APPLICANT**
Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan, 2555 W. Midway Blvd.
P. O. Box 446, Broomfield, CO 80038-0446

4. **NONPROPRIETARY NAME** Terazosin Hydrochloride

5. **AMENDMENTS AND OTHER DATES**
Geneva submitted the following telephone amendments since CR #4 was completed:

03/02/98	Re: Revision of Dissolution spec per FDA request
03/12/98	Re: Dissolution test results for 1 mg strength product.
03/19/98	Re: Dissolution test results for all strengths.

6. **PHARMACOLOGICAL CATEGORY** blood pressure regulator

7. **Rx or OTC** Rx

8. **DOSAGE FORM** Capsules

9. **POTENCY** 1 mg, 2 mg, 5 mg, 10 mg

10. **REVIEW NOTES AND COMMENTS**
Division of Bioequivalence revised the dissolution specs twice after the approval package was signed off by the Office of Chemistry Division I on 01/23/98. The spec in the first revision (letter to Geneva from DOB dated 02/13/98) is: NLT in 30 min (USP apparatus 2, paddle, at 50 rpm, 900 mL water). The spec in the second revision (dated 03/09/98) is: NLT in 60 min (USP apparatus 2, paddle, at 50 rpm, 900 mL water).

In 03/19/98 telephone amendment, Geneva provided dissolution test results for each strength using the latest (03/09/98) dissolution spec recommended by DOB. The 31 month ambient temperature and humidity dissolution data were generated from the ANDA batches in HPDE bottles. The data support 24 month expiration dating with the current DOB recommended specifications.

11. **CONCLUSIONS AND RECOMMENDATIONS**
The ANDA remains Approvable after the telephone amendments.

12. **REVIEWER** S. H. Liu, Ph.D.

DATE COMPLETED March 20, 1997.

cc: ANDA 74-823
ANDA DUP
Division File
Field Copy
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Endorsements:
HFD-623/S. Liu, Ph.D./03/20/98
HFD-623/V.Sayeed,Ph.D.

03/20/98
3/20/98

Office of Generic Drugs

Chemistry, Manufacturing and Control Review

1 CHEMISTRY REVIEW No. 4

2. ANDA # 74-823

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Attention: Beth Brannan
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4. LEGAL BASIS FOR ANDA SUBMISSIONS See CR #1.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME Terazosin Hydrochloride

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

9. AMENDMENTS AND OTHER DATES
12/12/97 Amendment (response to 12/05/97 Minor Fax)

10. PHARMACOLOGICAL CATEGORY
blood pressure regulator

11. Rx or OTC
Rx

12. RELATED IND/NDA
HYTRIN® (Abbott): NDA #20-347 (approved 12/14/94)

13. DOSAGE FORM Capsules

14. POTENCY 1 mg, 2 mg, 5 mg, 10 mg

15. CHEMICAL NAME AND STRUCTURE See CR #1.

16. RECORDS AND REPORTS N/A

17. COMMENTS CMC of the submission is now satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable

19. REVIEWER
S. Liu, Ph.D.

DATE COMPLETED
December 18, 1997.

DEC 5 1997

38. Chemistry Comments to be Provided to the Applicant:

ANDA: 74-823 APPLICANT: Geneva Pharmaceuticals, Inc.

DRUG PRODUCT: Terazosin Hydrochloride Capsules, 1 mg, 2 mg, 5 mg and 10 mg.

The deficiencies presented below represent MINOR deficiency.

is deficient. The has been notified of the deficiencies. Approval of your application is contingent on the correction of deficiencies. Please do not respond to this MINOR amendment until you have been notified by the holder of that they have responded to Agency's deficiency letter.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74823

BIOEQUIVALENCE REVIEW(S)

ANDA 74-823

MAY 17 1996

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 West Midway Blvd.
P.O. BOX 446
Broomfield CO 80038-0446

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Terazosin Hydrochloride Capsules 1 mg, 2 mg, 5 mg, and 10 mg (base)

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus 2 (Paddle) at 100 rpm. The test should meet the following specifications:

   Not less than of the labeled amount of the drug in the tablet is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

for Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.1
Liu,

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

DATE: 3-3-98

TO: ANDA 74-823 Terazocin Capsules by Geneva

FROM: Nancy Chamberlin, Pharm D.

SUBJECT: Dissolution specification time has been modified since we issued the 2-13-98 letter to the firm . In that letter we stated the dissolution method would need to be incorporated into their stability and quality control programs as:

Method: U.S.P. 23 apparatus 2 (paddle) at 50 rpm
Medium: 900 mL of water
Specification: NLT in 30 minutes

Discussions:
Dr. Makary informed me on 2-26-98 that our internal dissolution expert, Dr. Tran told him that the specifications for Terazocin capsules were changed. We are now recommending by the compendia staff to the PF and U.S.P. the following, which is now our interim specification:

Apparatus 2(paddle) 50 rpm NLT in 60 minutes

Recommendations:
I informed the firm on 2-26-98 per Dr. Makary's request that the specification has now been changed from minutes to inutes.

On 3-3-98 Beth Brannon called to notify us that they are able to meet the new specifications of NLT in 60 minutes with apparatus 2 (paddle). They submitted the data in writing on 3-3-98 for chemistry to look at the modified stability issue reflecting the change in the dissolution specifications.

Dr. Makary reviewed the 3-3-98 amendment with the corrected dissolution specifications and data, he found it acceptable. He will update the biosignoff sheet to reflect the new dissolution specification.

Concur:

_____ Date: 3/9/98
Moheb Makary, Ph. D. Acting Team Leader

Branch III, Division of Bioequivalence

____ Date: 3/9/98
Nhan Tran, Ph. D., Internal Dissolution Expert
Division of Bioequivalence

_____ Date: 3/9/98
Dale P. Conner, Pharm.D
Director
Division of Bioequivalence

CC: ANDA 74-823 Original and Dup
Division File
Bio File

x:\new\firmsam\geneva\memo\terazcon
Printed on 3-4-98 nc
Revised 3-9-98 nc

Geneva pharmaceuticals, inc.

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

(303) 466-2400

FEDERAL EXPRESS

MAR 0 3 1998

TELEPHONE AMENDMENT

ORIG AMENDMENT
N/Am

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 # 74-823 Terazosin Hydrochloride Capsules, 1 mg, 2 mg, 5 mg and 10 mg
Telephone Amendment - Chemistry: Change in dissolution specification and method

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for ANDA # 74-823 Terazosin Hydrochloride Capsules, 1 mg, 2 mg, 5 mg and 10 mg in accord with Section 505 (j) of the Federal Food, Drug, and Cosmetic Act and with 21 CFR Part 314.96 (a).

On February 13, 1998 we received a correspondence from the Division of Bioequivalence requesting a change to the dissolution specification and rpm speed. On February 26, 1998 in a subsequent telephone message from Nancy Chamberlin to Beth Brannan, the specification was further revised to the proposed Pharmacopeia Forum. In a telephone conversation with Jim Wilson and Dr. Sayeed on February 13, 1998 dissolution data was requested for the current ANDA batches with proposed specification. The original filed and requested information is:

Original	**Revised**
Paddles at **100 rpm**	Paddles at **50 rpm**
Specification: **NLT** .n 30 minutes	Specification: **NLT** .n **60** minutes

We are providing the updated Finished Product Specification and Data sheets and Stability protocols for each strength in Attachment 1.

The revised method reflecting the change in paddle speed and Q time is provided in Attachment 2. No other changes were made to the method.

Attachment 3 contains dissolution testing results for the ANDA batches of each strength.

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

Beth Brannan, Director
Drug Regulatory Affairs

Enclosures
BB/kak

RECEIVED
MAR 0 4 1998
GENERIC DRUGS

MAY 13 1996

Terazosin Hydrochloride
5 mg Capsule
ANDA # 74-823
Reviewer: Man M. Kochhar
74315SWD.

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
~~April 21~~, 1995
Dec. 29

REVIEW OF BIOEQUIVALENCE STUDY, WAIVER REQUEST, AND DISSOLUTION DATA

The purpose of this study is to compare the rate and extent of terazosin hydrochloride absorption in fasting healthy adult male volunteers following a single dose of 5 mg of test and reference product (Hytrin, Abbott). The protocol was designed for a two-way crossover, single dose bioequivalence study.

The firm is also requesting waiver of 1 mg, 2 mg, and 10 mg terazosin hydrochloride capsules.

BACKGROUND:

Terazosin hydrochloride is a quinazoline derivative. It is freely soluble in water and isotonic saline. Terazosin hydrochloride tablets are available in 1 mg, 2 mg, 5 mg and 10 mg strengths.

Terazosin hydrochloride is an antihypertensive agent which appears to exert its pharmacological effect by selective blockade of alpha-1-adrenoreceptors. Systolic and diastolic blood pressures are lowered in both the supine and standing positions. Orally administered terazosin is essentially completely absorbed in man. Nearly all of the circulating dose is in the form of parent drug. Food has little or no effect on bioavailability. The plasma levels of the free base peak in about 1 hour, and then decline, with a half-life of approximately 12 hours. Hepatic metabolism is extensive, with approximately 60% of the drug excreted via bile-feces, and 40% excreted in urine.

Terazosin can cause marked hypotension, especially postural hypotension, and syncope, in association with the first dose, or first few doses of therapy. Occasionally, the syncopal episode has been preceded by a bout of severe supraventricular tachycardia with heart rates of 120 to 160 beats per minutes.

IN-VIVO STUDY:

The objective of this study is to compare the relative bioavailability of terazosin hydrochloride 5 mg capsule (Geneva) with that of Hytrin 5 mg capsule (Abbott) in healthy male volunteers under fasting conditions.

The firm is requesting a waiver of 1 mg, 2 mg and 10 mg terazosin hydrochloride capsules based on the fasting study of 5 mg capsules.

The study was conducted by

protocol # B-03175

under the supervision of

STUDY DESIGN:

The fasting study was designed as a randomized, single dose (5 mg capsule), two-way crossover bioequivalence study under fasting conditions.

Subjects:

The study employed thirty-eight (38) healthy male volunteers between 18 and 45 years of age and within ±10% of the ideal body weight for their height and body frame (Metropolitan Insurance Company Bulletin, 1983). Volunteers without history of asthma, nasal polyps, or serious cardiovascular, hepatic, renal, hematopoietic, peptic ulcer or gastrointestinal disease, alcohol or drug abuse were employed.

Good health was ascertained from medical history, physical examination and routine laboratory tests (blood chemistry, hematology, urinalysis, etc.). The volunteers were not allowed to take any prescription medications and/or OTC preparations for at least two weeks prior to the start and until the end of the study. The volunteers were non smokers and not allowed to drink alcoholic beverages or caffeine-containing products for 48 hours prior to dosing and until study completion.
Blood pressure and heart rate were monitored prior to dosing and at 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 36 and 48 hours after the dose. Vital signs were measured at other times when it was deemed necessary.

The subjects were housed in the ıive-in facility from 10 hours before until 36 hours after the drug administration. The subjects returned for the blood draw at 48 and 60 hours.

The subjects fasted for 10 hours prior to and 4 hours after the drug administration. Water ad lib was allowed except within 2 hours of drug administration.

Method:

The product and dosage employed in this study were as follows:

A: Test: One 5 mg capsule terazosin hydrochloride (test drug), lot # 6495075 with 240 mL of water.
Batch Size: Expiry date: 8/97
Potency: 97%

B. Reference: One 5 mg capsule of Hytrin (Abbott), lot # 01-002-KP-21 with 240 mL of water. Expiry date: 4/96.
Potency: 99.2%

Ten (10) mL of venous blood were drawn in Vacutainers with EDTA at 0, 0.17, 0.33; 0.5, 0.75, 1, 1.5, 2, 3, 5, 8, 10, 12, 16, 24, 36, 48, and 60 hours. The plasma was separated and promptly frozen for analysis.

WASHOUT PERIOD: 1 Week

ANALYTICAL METHODOLOGY:

DATA ANALYSIS:

Individual analysis of variance (ANOVA with factors including drug, phase, sequence and subjects within sequence) were carried out to compare formulations at each sampling time, AUC (0-t), AUC (inf.), Cmax, Tmax, t1/2 and Kel. All ANOVAs were performed with SAS General Linear Models Procedures (GLM). 90% confidence intervals (two one-sided t-test) were calculated for terazosin pharmacokinetic parameters. For all analyses, effects were considered statistically significant if the probability associated with 'F' was less than 0.05.

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

All of the 38 subjects enrolled in the study completed the crossover. The plasma samples from 38 subjects were assayed for terazosin as per the protocol. The study was completed with no major protocol violations. The results of the study comparing the bioavailability of terazosin are given in Table 1 and 2. The mean plasma terazosin concentrations are given in Figure 1.

TABLE 1

Mean Plasma Concentration of Terazosin (N=38)

Time (hours)	Geneva's Terazosin Lot # 6495075 ng/mL (CV%)	Abbott's Hytrin Lot # 01-002-KP-21 ng/mL (CV%)	T/R
0	0.0 (-)	0.0 (-)	0.0
0.17	0.0 (---)	0.09 (434)	0.0
0.33	27.78 (120)	18.55 (160)	1.49
0.5	71.19 (63)	50.63 (89)	1.40
0.75	95.59 (37)	72.08 (52)	1.32
1	98.61 (30)	82.99 (40)	1.19
1.5	92.95 (27)	85.67 (31)	1.08
2	91.02 (27)	83.26 (28)	1.09

3	85.12 (24)	82.52 (27)	1.03
5	65.23 (26)	64.48 (26)	1.01
8	47.54 (26)	45.57 (27)	1.04
10	38.50 (26)	37.54 (27)	1.02
12	31.45 (28)	31.11 (29)	1.01
16	23.53 (29)	23.77 (31)	0.99
24	14.45 (32)	13.58 (31)	1.06
36	7.13 (53)	6.38 (34)	1.11
48	3.54 (42)	3.55 (41)	1.00
60	2.02 (52)	1.94 (47)	1.04

Table 2

A Summary of Pharmacokinetic Parameters for 38 subjects
TERAZOSIN

Parameters	**Geneva's Terazosin**	**Abbott's Hytrin**	**T/R**	**90% Confidence Interval**
AUC_{0-60} ng.hr/mL	1201.0 (25)	1144.1 (24)	1.05	101; 109
AUC_{0-inf} ng.hr/mL	1238.7 (26)	1179.8 (24)	1.05	101; 109
C_{max} ng/mL	113.1 (26)	105.7 (24)	1.07	102; 112
T_{max} (hours)	1.08 (55)	1.41 (74)	0.76	
$t_{1/2}$ (hours)	11.6 (13)	11.7 (11)	0.99	
K_{el} (1/hour)	0.061(13)	0.060(11)	1.01	
Ln AUC_{0-60} ng.hr/mL	7.06(4)	7.01(4)		101; 109
Ln AUC_{inf} ng.hr/mL	7.09(4)	7.04(4)		101; 109
Ln C_{max}	4.69(6)	4.63(5)		102; 112

The terazosin AUC_{0-t} and AUC_{0-inf} produced by Geneva's formulation were 5% higher than the values for the reference drug. The C_{max} was 7% higher than the reference. T_{max} was 23.4% lower for the test drug. $t_{1/2}$ and K_{el} values differ only by less than 1.6%. ANOVA performed on the plasma terazosin concentration data at each of the eighteen sampling times detected statistically significant

differences 0.33, 0.5 and 0.75 hours between the two formulations. The firm did calculate Ln AUC and Ln Cmax for terazosin and the 90% confidence intervals for log-transformed parameters were 101 to 109 for Ln AUC0-t, 101 to 109 for Ln AUCinf, and 102 to 112 for Ln Cmax.

The 90% confidence interval for terazosin for AUC_{0-60} and AUC_{0-inf} and C_{max} were well within ±20% limits set for defining product bioequivalence, in a fasting study.

There were minor adverse events reported; cough (1-dry), abdominal pain (3- stomachache), dry vomit (2- dry heaves), dizziness and lightheadedness (31), headache (4), mouth dry (1- dry mouth); Fever (1), nausea (9), chest pain (1). There were no serious adverse effects which required dropping any subjects from the study or required therapeutic medical intervention.

On the basis of fasting in vivo bioavailability data it is determined that Geneva's terazosin hydrochloride 5 mg capsules and Abbott's Hytrin 5 mg capsules are bioequivalent under fasting conditions.

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 900 mL of water at 37°C using USP XXIII apparatus 2 (paddle) at 100 rpm. Results are presented in Table 3. Both the test and reference products meet the dissolution specifications of not less than of the labeled amount of drug dissolved from the tablets in 30 minutes.

The batch size was capsules.

COMMENTS:

1. The study was conducted in 38 healthy volunteers comparing the plasma concentrations from Geneva's terazosin hydrochloride 5 mg capsules to that of reference Hytrin 5 mg capsules manufactured by Abbott. The terazosin AUC_{0-60}, AUC_{o-inf}, C_{max} of the Geneva's formulation were 4.97% higher, 4.99% higher, and 7% higher respectively than the corresponding Abbott's reference values. ANOVA performed on the plasma terazosin concentration data detected statistically significant differences at 0.33, 0.5 and 0.75 hours between two formulations. These results indicate that the test drug is bioequivalent to the reference product under fasting conditions.

2. Analysis of variance indicated no statistical significant treatment differences or group-by-sequence effect for AUC and Cmax for terazosin. The 90% confidence intervals were well within the limits of ±20%.

3. The validation studies conducted by the sponsor for terazosin are acceptable to the Division of Bioequivalence.

4. The elimination of terazosin from the plasma appeared to be biphasic for most of the subjects. The elimination rate constants were estimated from the plasma terazosin data for all subjects using the plasma concentrations of the final elimination phase as best as could be determined from the plasma drug concentration vs time plots (log scale) for the individual subjects. The half-life values and areas under the concentration-time curves to infinity using the elimination rate constants.

5. Sitting blood pressure and heart rate measurements were monitored at approximately 1, 2, 3, 4, 6, 8, 12, 24 and 36 hours after drug administration. Analysis of the blood pressure and heart rate data resulted in no statistically significant differences between products in the baseline, minimum or drop from baseline for diastolic pressure, systolic pressure, or heart rate. ANOVA detected the 2% difference for baseline systolic blood pressure, the 23% difference for the drop in systolic blood pressure, the 3% difference in baseline heart rate between dosing periods as significant. these differences were very small, but were detected as significant due to high study power. These are illustrated in Figure 2, 3, and 4.

6. The firm is requesting a waiver of 1 mg, 2 mg and 10 mg terazosin hydrochloride capsules based on the fasting study of 5 mg capsule. The waiver for the higher strength (10 mg) can be granted because of hypotension, especially postural hypotension, and syncope, in association with the first dose. Therefore, the waiver for 1 mg, 2 mg and 10 mg is granted based on an acceptable fasting study of 5 mg capsule.

7. The in vitro dissolution testing conducted for 1 mg, 2 mg, 5 mg and 10 mg capsules of the test and reference products shows greater than of the labeled amount of the terazosin hydrochloride dissolved in 30 minutes.

8. The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

9. The in vivo fasting bioequivalence study is acceptable.

10. The firm has demonstrated that the formulations of its terazosin hydrochloride capsules, 1 mg, 2 mg, 5 mg and 10 mg, are proportional with respect to active and inactive ingredients (Table 4).

DEFICIENCY: None

RECOMMENDATIONS:

1. The fasting bioequivalence study conducted by Geneva Pharmaceuticals on its Terazosin Hydrochloride 5 mg capsules, lot # 6495075, comparing it to Hytrin 5 mg capsules, lot # 01-002-KP-21 manufactured by Abbott Laboratories have been found acceptable

by the Division of Bioequivalence. The study demonstrates that under fasting conditions the Geneva's Terazosin Hydrochloride 5 mg capsules are bioequivalent to the reference product, Hytrin 5 mg capsules manufactured by Abbott.

2. The formulations for 1 mg, 2 mg, 10 mg Terazosin Hydrochloride capsules are proportionally similar to 5 mg Terazosin Hydrochloride capsule which underwent bioequivalent study. The waiver of in vivo bioequivalence study requirement for Geneva Pharmaceuticals 1 mg, 2 mg, and 10 mg capsules is granted. The 1 mg, 2 mg, and 10 mg Terazosin Hydrochloride capsules from Geneva Pharmaceuticals are, therefore, deemed bioequivalent to 1 mg, 2 mg, and 10 mg Hytrin capsules manufactured by Abbott based on 21 CFR 320.22 (d) (2).

3. The in vitro test results are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs.The dissolution testing should be conducted in 900 mL of water at 37°C using USP XXII apparatus 2 (Paddle) at 100 rpm. The test should meet the following specifications:

> Not less than of the labeled amount of the drug in the tablet is dissolved in 30 minutes.

4. From the bioequivalence point of view, the firm has met the requirements for in vivo bioequivalence and in vitro dissolution test, and therefore, the application is approvable.

The firm should be informed of the recommendations.

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE 5/8/96

Concur: _____ Date: 5/13/96
for Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

MMKochhar/mmk/4-15-96; 5-6-96; A:74-823 BIO

cc: ANDA # 74-823 original, HFD-630, HFD-600 (Hare), HFD-344 (CViswanathan), HFD-658 (Mhatre, Kochhar), Drug File, Division File.

(Please select Typeover for Input.)

Table 3. In Vitro Dissolution Testing

Drug (Generic Name):Terazosin HCl capsules
Dose Strength: 5 mg, Lot # 64950575
ANDA No.:74-823
Firm:Geneva Pharmaceuticals
Submission Date:1/2/96
File Name:

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle:x RPM: 100
No. Units Tested: 12
Medium: Water Volume: 900 mL
Specifications:NLT in 30 Min
Reference Drug: Abbott's Hytrin capsules. Lot #01-002-KP21
Assay Methodology

II. Results of In Vitro Dissolution Testing:

Sampling Times Minutes	Test Product Lot # 6495075 Strength(5 mg)			Reference Product Lot # 01-002-KP21 Strength(5 mg)		
	Mean %	Range	%RSD	Mean %	Range	%RSD
10	99		3.1	106		1.2%
20	100		1.6	106		0.6
30	100		1.4	106		0.8
40	100		1.6	106		0.7

Sampling Times Minutes	Test Product Lot # 6495077 Strength(10mg)			Reference Product Lot # 01-006-KP21 Strength(10mg)		
	Mean %	Range	%RSD	Mean %	Range	%RSD
10	98		1.7	103		1.4
20	99		1.6	104		0.9
30	99		1.7	103		0.9
40	99		1.7	104		0.7

Sampling Times Minutes	Test Product Lot # 6495074 Strength(2 mg)			Reference Product Lot # 89-331-AF21 Strength(2 mg)		
	Mean %	Range	%RSD	Mean %	Range	%RSD
10	86		14.1	104		14.7
20	99		3.7	113		1.4
30	100		2.2	113		2.1
40	100		2.0	114		1.7

Sampling Times Minutes	Test Product Lot # 6493048 Strength(1 mg)			Reference Product Lot # 89-335-AF21 Strength(1 mg)		
	Mean %	Range	%RSD	Mean %	Range	%RSD
10	93		10.8	118		6.6
20	103		1.7	122		1.3
30	102		1.5	122		1.1
40	101		0.9	121		1.2

TABLE 4

FORMULATION

Ingredients	1 mg	2 mg	5 mg	10 mg
	mg per tablet			
Terazosin HCl*	1.095	2.189	5.471	10.942
Lactose Monohydrate NF				
Microcrystalline Cellulos				
Crosprovidone NF				
Magnesium Stearate NF				
#3 Opaque Pink Cap/Opaque Pink Body,Imprinted GG623 in Black Ink				
#3 Opaque White Cap/ Opaque White Body				
#3 Opaque Yellow Cap/ Opaque Yellow Body				
#3 Opaque Aqua Cap/ Opaque Aqua Body				
Corn Starch				
TOTAL	273.00	273.00	273.00	273.00

* equivalent to 1 mg, 2 mg, 5 mg, and 10 mg terazosin respectively

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74823

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 74-823 **DRUG PRODUCT:** Terazosin Hydrochloride

Applicant: Geneva Pharmaceuticals, Inc.

DOSAGE FORM: Capsules **STRENGTH:** 1 mg, 2 mg, 5 mg, 10 mg

CGMP STATEMENT/EIR UPDATE STATUS: EER acceptable 06/04/97.

BIO STUDY: Bio review was completed on 05/13/96. Acceptance letter with recommended dissolution specs was issued on 05/17/96. Geneva provided comparative dissolution profiles for the original and revised process (mixing time). Values of f_2 calculations were provided and acceptable.

VALIDATION: Method validation was conducted by Denver-DO (05/19/97), and was found satisfactory (with recommendation) (CR #2).

STABILITY: Three months accelerated stability data were submitted for the four new executed batches (see CR #2, and CR #3).

Containers used in the studies are identical to those in the container section.

LABELING: Acceptable per labeling review dated 12/17/97 (C.Holquist).

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH: capsules (lot #6495075, 5 mg strength)

Bulk Drug Substance Source: is still Adequate as of 12/18/97

SIZE OF STABILITY BATCHES: Same as the biobatch

PROPOSED PRODUCTION BATCH: Manufacturing process is same as the biobatch. Batch sizes for intended maximum production are as follows:

capsules for the 1 mg strength.
capsules for the 2 mg strength.
capsules for the 5 mg strength.
capsules for the 10 mg strength.

REVIEWER: S. Liu, Ph.D. **DATE COMPLETED:** 12/18/97

12/18/97

HFD-623/S.Liu, Ph.D
HFD-623/V.Sayeed, P...D.
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F/T by: gp/1/2/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74823

CORRESPONDENCE

Geneva pharmaceuticals, inc.

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

(303) 466-2400

FEDERAL EXPRESS

MAR 19 1998

TELEPHONE 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

N/AM

RE: ANDA # 74-823 Terazosin Hydrochloride Capsules, 1 mg, 2 mg, 5 mg and 10 mg
Telephone Amendment - Chemistry: Stability

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting a telephone amendment to our unapproved Abbreviated New Drug Application for ANDA # 74-823 Terazosin Hydrochloride Capsules, 1 mg, 2 mg, 5 mg and 10 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 a telephone conversation with Beth Brannan of Geneva and Jim Wilson and Dr. Sayeed of FDA, on March 19, 1998. FDA requested that Geneva provide dissolution data for the 2 mg, 5 mg, and 10 mg strengths to support 24 month expiration dating with the new Division of Bioequivalence recommended conditions and specification.

We are providing dissolution test results for each of the ANDA strengths on the attached table. The data represents 31 months at ambient conditions in HDPE bottles. The formulations for all strengths are equivalent.

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

Beth Brannan, Director
Drug Regulatory Affairs

Enclosures
BB/kak

RECEIVED
MAR 20 1998
GENERIC DRUGS

3/13/98

4.1

eneva
harmaceuticals, inc.

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

FEDERAL EXPRESS

MAR 1 2 1998

TELEPHONE 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

ORIG AMENDMENT

RE: ANDA # 74-823 Terazosin Hydrochloride Capsules, 1 mg, 2 mg, 5 mg and 10 mg
Telephone Amendment - Chemistry: Stability

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting a telephone amendment to our unapproved Abbreviated New Drug Application for ANDA # 74-823 Terazosin Hydrochloride Capsules, 1 mg, 2 mg, 5 mg and 10 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 a telephone conversation with Archie Phillips of Geneva and Jim Wilson and Dr. Sayeed of FDA, on March 12, 1998. FDA requested that Geneva provide dissolution data to support 24 month expiration dating with the new Division of Bioequivalence recommended conditions and specification.

We are providing dissolution test results for the 1mg strength original ANDA batch, lot 6495073. The data for the 1 mg strength represents 31 months at ambient conditions in HDPE bottles. The formulations for all strengths are equivalent.

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.

A. Phillips for Beth Brannan

Beth Brannan, Director
Drug Regulatory Affairs

Enclosures
BB/kak

RECEIVED
MAR 1 3 1998
GENERIC DRUGS

Geneva pharmaceuticals, inc.

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

(303) 466-2400

FEDERAL EXPRESS

DEC 12 1997

MINOR AMENDMENT

FPL satisfactory
C. Holquist
12/17/97

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

NDA ORIG AMENDMENT

RE: ANDA Number: 74-823, Terazosin Hydrochloride Capsules 1 mg, 2 mg, 5mg, 10 mg
Minor Amendment -- (Chemistry and Labeling)

Dear Director:

Geneva Pharmaceuticals, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for 74-823, Terazosin Hydrochloride Capsules 1 mg, 2 mg, 5mg, 10 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 FDA correspondence provided by facsimile dated December 5, 1997. Response to comments are provided below in the order of appearance in your correspondence. Reference is also made to a telephone conversation on 12/10/97 between FDA Label reviewer Carol Holquest and Geneva DRA Associate Kathy Kropp.

Chemistry

Geneva acknowledges the We contacted on 12/8/97. In this conversation indicated that a response was sent to the FDA to the attention of Dr. Shing Liu on 11/25/97.

Labeling

1. GENERAL COMMENT

No response needed.

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2. CONTAINER

As per a phone conversation on 12/10/97 with FDA Label reviewer Carol Holquest and Geneva DRA associate Kathy Kropp, Geneva is updating the storage statement on container labels, as well as on the outsert and patient package insert as follows:

Store at controlled room temperature between 15°-30°C (59°-86°F)

3. INSERT

The physician insert and the patient information insert have been updated as requested.

Container labels, physician insert and patient information insert are submitted in final print.

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

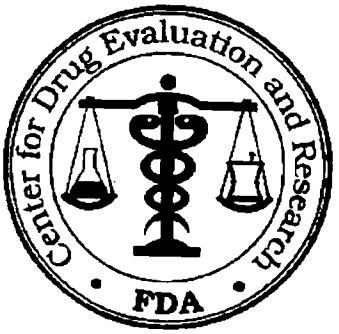
Enclosures

BB/kak

MINOR AMENDMENT

DEC 5 1997

ANDA 74-823



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Geneva Pharmaceuticals, Inc. PHONE: 303-466-2400

ATTN: Beth Brannan FAX: 303-438-4600

FROM: James Wilson PROJECT MANAGER (301) 827–5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 29, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Terazocin Hydrochloride Capsules 1 mg,2 mg, 5 mg and 10 mg.

Reference is also made to your amendment(s) dated 7/17/97 and 8/1/97.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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 of the deficiencies listed. Facsimiles or partial replies will not be considered for review, norwill the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/~~will be~~ notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

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