

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
74530

CORRESPONDENCE

AUG 14 1998

Zenith Goldline Pharmaceuticals, Inc.
Attention: Jason A. Gross
140 Legrand Avenue
Northvale, NJ 07647
|||||

Dear Sir:

This is in reference to your abbreviated new drug application dated August 1, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Terazosin Hydrochloride Tablets, 1 mg (base), 2 mg (base), 5 mg (base) and 10 mg (base).

Reference is also made to your amendments dated July 12, 1995; January 8, February 12, and April 15, 1997; and, June 3 and June 29, 1998.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention.

The listed drug product referenced in your application is subject to a period of patent protection which expires on April 29, 2013, (Patent No. 5,504,207). Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated application shall be made effective immediately unless an action is brought before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. You have notified FDA that Zenith Goldline Pharmaceuticals has complied with the requirements of Section 505(j)(2)(B) of the Act by providing the required notice to each patent holder, and that no action for patent infringement was brought against Zenith Goldline Pharmaceuticals within the statutory forty-five day period.

However, the Act provides that an abbreviated application that contains a certification described in section 505(j)(2)(A)(vii)(IV) (a "paragraph IV certification") and that is for a drug for which a previous abbreviated application has been submitted, that also contains a paragraph IV certification, shall be made effective not earlier than one hundred and eighty days after:

1. the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or
2. the date of a decision of a court holding the patent which is the subject of the certification to be invalid or not infringed,

whichever is earlier (section 505(j)(5)(B)(iv)).

In this instance, a previous abbreviated application for Terazosin Hydrochloride Tablets, 1 mg (base), 2 mg (base), 5 mg (base) and 10 mg (base), with a paragraph IV certification, has been submitted. Accordingly, your application will be eligible for final approval beginning on the date that is one hundred and eighty days after the date the Agency receives notice of the first commercial marketing of the drug under the previous application, or the date of a court decision described under section 505(j)(5)(B)(iv), whichever is earlier. We refer you to the Agency's recently issued guidance document "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998), for additional information.

Because the Agency is granting a tentative approval for this application, when your application may be considered for final approval, you must amend your application. The Agency will provide you written notice of the information needed to determine the earliest possible final approval date of your application under section 505(j)(5)(B)(iv) as soon as such information becomes available. Your amendment, which must be submitted at least 60, but not more than 90 days prior to final approval must then provide:

1. updated information related to labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

2. a statement that no such changes have been made to the application since the date of tentative approval.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

The amendment should be designated as a MINOR AMENDMENT in your cover letter. Before you submit the amendment, please contact Joseph Buccine, Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours, A

/S/

8/13/98 -

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

Terazosin Hydrochloride Tablets
ANDA 74-530

Zenith Laboratories Inc.
Attention: Nicholas Maselli
Department of Regulatory Affairs
140 Legrand Avenue
Northvale, NJ 07647

FEB 24 1995

Dear Mr. Maselli:

Reference is made to the fasting bioequivalence study, *in vitro* dissolution and *in vivo* bioequivalence waiver requests submitted on August 1, 1994, for Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg.

The Office of Generic Drugs has reviewed the referenced material and have found the data comparing the test product with the reference listed drug Hytrin® Tablet, manufactured by Abbott Laboratories to be incomplete for the following reason:

The *in vitro* dissolution testing was not conducted in accordance with approved FDA methodology. The methodology utilized is acceptable with the exception of the medium, which should be water instead of . Please conduct comparative dissolution testing for all strengths, utilizing the FDA methodology, and submit the results for review.

The *in vivo* bioequivalence waiver requests for the 1 mg, 2 mg, and 10 mg products cannot be considered until the required *in vitro* dissolution testing is found acceptable. The request for waivers should be resubmitted with the amendment.

You are required to take an action described under 21 CFR 314.96 which will amend this application.

If you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,


Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

ANDA 74-530

Zenith Laboratories
Attention: Mr. Nicholas Maselli
140 Legrand Avenue
Northvale, NJ 07647

JAN 5 1995

Dear Sir:

This is in reference to your abbreviated new drug application dated August 1, 1994, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg of Terazosin.

Reference is also made to your amendment dated September 12, 1994.

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

A. Chemistry Deficiencies:

1. Please add a test for the identification of ^{to} the testing protocol of terazosin hydrochloride drug substance. In addition, please provide the particle size distribution profile for batch PD-0822.
2. Please provide new COAs, from yourself and your supplier, which demonstrate that Lactose meets the new monograph for Lactose Monohydrate NF (USP 23/NF 18, p2258). In addition, please update the specifications for lactose to the USP monograph, and add tests and specifications for particle size distribution and tapped density to your testing protocol.
3. Please add tests and specifications for particle size profile and tapped density to your testing protocol for corn starch.
4. Please provide comparative IR spectra for crospovidone (sample vs. reference).
5. Please provide a COA for Colloidal Silicon Dioxide, which demonstrates that the excipient meets the specifications for organic volatile impurities.

6. Please provide reference and sample IR spectra for the colors Titanium Lake Blend (pink) and Pigment Blend Yellow. Please also demonstrate that Pigment Blend Yellow meets the specifications set forth in 21 CFR 73.1200 of the regulations for arsenic, lead and mercury. Please also demonstrate that elemental iron in the 5 mg tablet consumed with the prescribed dosage shall not exceed 5 mg/day.
7. Please provide data to demonstrate that Magnesium Stearate NF passes the required test for Organic Volatile Impurities.
8. Please describe exactly where in the blend each dosage unit was sampled for blend uniformity. Please justify that the number of samples taken is sufficient to determine the uniformity of the active ingredient in each of the blends that were manufactured for this application. We request that the specification for the mean, whether it be the mean of 10, 30 or some other number of units tested, is between 90.0% and 110.0%, and the specification for individual units is between 85.0% and 115.0%.
9. Please provide specifications for the in-process blend tests of pour bulk density, tapped bulk density and moisture.
10. Please provide the individual, rather than average, in-process tablet data for hardness, thickness and weight variation from each of the batches that were manufactured for this application. This data may be provided on control charts.
11. Please add a second identification test for Terazosin Tablets. The second test should be able to identify the structure of the active ingredient. We recommend infrared spectrophotometry.
12. The system suitability tests in methods,
should include specifications for tailing (t), resolution (R) and column efficiency (theoretical plates) (N). The resolution factor should be determined between the terazosin peak and the peak for
13. The release specification for
should be changed to a specification for any individual impurity or degradant and reduced from NMT % to NMT % each. The specification for total impurities should remain as is.

14. Please explain why the in-process and release data for uniformity of dosage units and dissolution are the same. Please provide new COAs for batches ND-190 (1 mg), ND-192 (2 mg), ND-193 (5 mg), and ND-194 (10 mg), if appropriate.
15. Please include a request for a categorical exclusion under 21 CFR 25.24(c)(1) of the regulations, or file an appropriate environmental assessment as described under the same set of regulations.

B. Labeling Deficiencies:

CONTAINER (100s, 500s, and 1000s):

1. The strength of this product is expressed in terms of terazosin and should be clarified as such. This could be accomplished by several means. The first would be to include an asterisk after the strength on the main panel and before the "Each tablet contains" statement on the side panel. The second would be as follows -

1 mg
(terazosin)

or

equivalent to **1 mg** terazosin

2. We encourage you to differentiate your various product strengths by the use of contrasting colors, boxing, etc.

INSERT:

1. **GENERAL COMMENT**

Use "terazosin" rather than "terazosin hydrochloride" or "terazosin hydrochloride tablets" throughout the insert except in the following sections (unless otherwise noted) -

DESCRIPTION
DOSAGE AND ADMINISTRATION
HOW SUPPLIED

2. DESCRIPTION

- a. Revise the molecular weight to read -

423.89

- b. Paragraph 2 (second sentence) -

Each tablet for oral administration, contains terazosin hydrochloride equivalent to 1 mg, 2 mg, 5 mg or 10 mg terazosin. In addition, each tablet contains the following inactive ingredients...

- c. In the list of inactive ingredients, identify the dyes contained in Pink Titanium Lake Blend and Yellow Pigment Blend.

3. INDICATIONS AND USAGE (second sentence) -

They can be used alone...

4. PRECAUTIONS

- a. Prostatic Cancer

Delete this entire subsection.

- b. Orthostatic Hypotension, add as last sentence -

Patients with occupations in which such events represent potential problems should be treated with particular caution.

- c. Drug Interactions (third sentence) -

Delete the line space between item #2 and item #3.

- d. Carcinogenesis, Mutagenesis, Impairment of Fertility

- 1) Paragraph 2 -

Terazosin administered in the feed to rats at doses of 8, 40, and 250 mg/kg/day (70, 350, and 2100 mg/m²/day), for two years,...to the 250 mg/kg dose. This dose is 175 times the maximum recommended human dose of 20 mg (12 mg/m²). Female rats were unaffected.

- Terazosin was not oncogenic...at a maximum tolerated dose of 32 mg/kg/day (110 mg/m²; 9 times the maximum recommended human dose). The absence of...

2) Paragraph 3 (second sentence) -

Four of 20 male rats given 30 mg/kg (240 mg/m²; 20 times the maximum recommended human dose), and five of 19 male rats given 120 mg/kg (960 mg/m²; 80 times the recommended human dose), failed to sire a litter.

3) Paragraph 4 -

Oral administration of terazosin for one or two years elicited a statistically significant increase in the incidence of testicular atrophy in rats exposed to 40 and 250 mg/kg/day (29 and 175 times the maximum recommended human dose), but not in rats exposed to 8 mg/kg/day (>6 times the maximum recommended human dose). Testicular atrophy was also observed in dogs dosed with 300 mg/kg/day (>500 times the maximum recommended human dose) for three months but not after one year when dosed with 20 mg/kg/day (38 times the maximum recommended human dose). This lesion has also been seen with prazosin hydrochloride, another (marketed) selective alpha-1 blocking agent.

e. Pregnancy

Teratogenic Effects: Pregnancy Category C

Terazosin was not teratogenic in either rats or rabbits when administered at oral doses up to 280 and 60 times, respectively, the maximum recommended human dose. Fetal resorptions occurred in rats dosed with 480 mg/kg/day, approximately 280 times the maximum recommended human dose. Increased fetal absorptions, ...in offspring of rabbits dosed with 60 times the maximum recommended human dose. These findings...

Nonteratogenic effects

...more pups died in the group dosed with 120 mg/kg/day (>75 times the maximum recommended human dose)...

f. The subsection headings "Nursing Mothers" and "Pediatric Use" should appear with the same prominence as the other subsection headings.

5. ADVERSE REACTIONS

- a. In Table 1 and Table 2, delete "HYPERTENSION" from the title.
- b. In Table 1, relocate the "+" to appear closer to "Asthenia".
- c. In Table 2 -

DISCONTINUATIONS (plural)

6. DOSAGE AND ADMINISTRATION, add the following to appear at the end of this section -

Use with other drugs.

Caution should be observed when terazosin is administered concomitantly with other antihypertensive agents, especially the calcium channel blocker verapamil, to avoid the possibility of developing significant hypotension. When using terazosin and other antihypertensive agents concomitantly, dosage reduction and retitration of either agent may be necessary (see PRECAUTIONS).

7. HOW SUPPLIED

- a. Indicate whether the tablets are unscored or scored.
- b. ...on the other side containing terazosin hydrochloride, equivalent to __ mg terazosin, packaged in...

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

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. We acknowledge submission of a process validation protocol. Please note that the final determination of the adequacy of the process validation data is the responsibility of the District Office.
2. Please provide any additional 25-30°C stability data available.
3. Validation of your analytical method package will be delayed until the Division of Bioequivalence finds the dissolution method acceptable. A satisfactory validation is required 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 MAJOR amendment and should be so designated in your cover letter. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/

1/4/85
Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-530
DUP File
Division File
Field Copy
HFD-600/Reading File

NOT APPROVABLE - MAJOR AMENDMENT

ANDA 74-530

DEC 18 1995

Zenith Goldline Pharmaceuticals
Attention: Robert J. Monaghan
140 Legrand Avenue
Northvale NJ 11413

Dear Sir:

Reference is made to your abbreviated new drug application dated August 1, 1994, submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Terazosin Hydrochloride Tablets 1 mg, 2 mg, 5 mg, and 10 mg.

The following comments pertain only to bioequivalency issues in the August 1, 1994 and July 12, 1995 submissions.

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 at 50 rpm. The test products should meet the following specifications:

Not less than % of the labeled amount of terazosin in the dosage form 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,

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

Zenith Laboratories, Inc.
Attention: Robert J. Monaghan
140 Legrand Avenue
Northvale, NJ 07647

MAR 20 1996

Dear Sir:

This is in reference to your abbreviated new drug application dated August 1, 1994, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg mg of Terazosin.

Reference is also made to your amendments dated July 18, 1995.

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

Labeling Deficiencies

1. **CONTAINER** (100s, 500s, and 1000s): Satisfactory in FPL.
2. **INSERT:**
 - a. **DESCRIPTION**

Delete from the structural formula.
 - b. **CLINICAL PHARMACOLOGY, Pharmacokinetics** (first sentence) -

Relative to solution, terazosin administered as tablets is...
 - c. **INDICATIONS AND USAGE**

Terazosin hydrochloride tablets are...
 - d. **PRECAUTIONS**
 - A) **Drug Interactions**
 - i) line 1 -

..., terazosin has been...

ii) line 11 -

methyclothiazide (spelling)

B) Pediatric Use

...in pediatric patients have not...

e. ADVERSE REACTIONS

The first two paragraphs should be combined to appear as one paragraph.

f. DOSAGE AND ADMINISTRATION

Use "terazosin" rather than "terazosin hydrochloride" throughout this section.

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

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

On completion of the validation of this ANDA for both the Drug Substance and the 5 mg Tablets, the FDA Analyst had these comments and concerns about Analytical Method

1. There should be a statement in the method indicating that only one injection will be made on each sample and standard vials. (No multiple injections on one vial should be made.)
2. The Split Vent Flow rate for the column should be specified before adjusting the flow rate from the Head Space Autosampler.

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/

3/19/66

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

cc: ANDA #74-530
ANDA #74-530/DUP/Division File
Field Copy
HFD-600/Reading File

Not Approvable - Minor

ANDA 74-530

Zenith Goldline Pharmaceuticals, Inc.
Attention: Karen Rocco
140 Legrand Avenue
Northvale, NJ 07647

Dear Ms. Rocco:

This refers to your abbreviated new drug application dated August 1, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Terazosin Hydrochloride Tablets, 1 mg, 2mg, 5mg and 10 mg.

Reference is also made to your amendment dated April 25, 1996.

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

In accord with 21 CFR 314.127(a)(12) we are refusing to approve this application because it does not meet the requirements under section 505(j)(2)(A) of the Act. Specifically, you have failed to amend this application to provide patent certifications for Patent Nos. 5,504,207 and 5,412,095, each expiring on April 29, 2013 as listed in the 17th Edition of Approved Drug Products with Therapeutic Equivalence Evaluations. A certification is required with respect to each timely filed patent which claims the listed drug or which claims a use for such listed drug for which the applicant is seeking approval and for which information is required to be filed under section 505(b) or (c) of the Act. We refer you to 21 CFR 314.94(a)(12) for further guidance.

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/

7/8/97

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

JUN 24 1998

Zenith Goldline Pharmaceuticals, Inc.
Attention: Jason Gross
140 Legrand Avenue
Northvale, NJ 07647

Dear Sir:

This refers to your abbreviated new drug application dated August 1, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Terazosin Hydrochloride Tablets, 1 mg, 2mg, 5mg and 10 mg.

Reference is also made to your amendment dated April 9, 1998, providing Paragraph IV patent certifications for US. Patent Nos. 5,504,207 and 5,412,095. Reference is also made to a telephone conversation on June 15, 1998 between Jason Gross of the firm and Jerry Phillips/Peter Rickman of the agency and your correspondence dated June 16, 1998.

In accordance with 21 CFR 314.95(a), for each patent that claims the listed drug or that claims a use for such listed drug for which an applicant is seeking approval and that the applicant certifies under 21 CFR 314.94(a)(12) is invalid, unenforceable, or will not be infringed, the applicant shall send notice of such certification by registered or certified mail, return receipt requested to both the owner of the patent and the holder of the approved application under section 505(b) of the Act. In addition, we refer you to 21 CFR 314.107(f)(3) which provides the form used when the patent owner or approved application holder waives its opportunity to file a legal action for patent infringement within 45 days of a receipt of the notice of certification. In the form, the patent owner or exclusive patent licensee must acknowledge receipt of notice. Therefore, the application is deficient and, therefore, not approvable under Section 505(j)(2)(A) of the Act for the following reasons:

1. **SENDING THE NOTICE**

In accordance with 21 CFR 314.95(a) you must:

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

- 1) Each owner of the patent or the representative designated by the owner to receive the notice;
- 2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

2. **DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE**

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).
- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

3. **DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME**

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.
- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day

period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

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,

in 1 1
/S/

6/24/98

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



Zenith Goldline
PHARMACEUTICALS

Regulatory Affairs

MAR 24 2000

March 24, 2000

Mr. Gary J. Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-600)
Metro Park North II
7500 Standish Place, Room 286
Rockville, MD 20855

FA

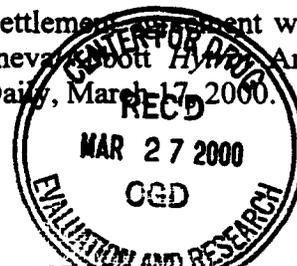
Re: Zenith Goldline Terazosin HCl Tablets, 1 mg (base), 2 mg (base), 5 mg (base),
10 mg (base): ANDA 74-530

Dear Mr. Buehler:

The above ANDA received tentative approval on August 14, 1998. The tentative approval letter stated that Zenith Goldline Pharmaceuticals' (Zenith) ANDA was not the first ANDA for terazosin HCl tablets, and, therefore, its ANDA would not be eligible for approval until the occurrence of specified events outside Zenith's control. The letter went on to state that Zenith could submit an amendment requesting final approval of its ANDA when the application "may be considered for final approval." The letter also stated: "The Agency will provide you written notice of the information needed to determine the earliest possible final approval date of your application under section 505(j)(5)(B)(iv) as soon as such information becomes available."

To date, Zenith has received no notice of the information it needs to determine the earliest possible final approval date. For that reason, Zenith Goldline has been unable to determine when it should submit an amendment requesting final approval of its ANDA.

Zenith hereby requests that you send the notice described in your August 14, 1998 letter. According to the trade press, Geneva Pharmaceuticals, Inc., whose ANDA for terazosin HCl tablets was approved on December 31, 1998, has entered into a settlement agreement with the Federal Trade Commission. See the attached news item "Geneva's Abbott Hyatt Antitrust Settlement Will Allow Launch of Generic Tablets," Health News Daily, March 17, 2000.



140 Legrand Ave., Northvale, New Jersey 07647 • (201) 767-1700 (800) 387-0122 Fax: (201) 767-3804

Miami, FL • Walton, KY • Cidra, P.R. • St. Croix, U.S. VI.

Mr. Gary J. Buehler
March 24, 2000
Page 2

Geneva's tablet ANDA was the "previous abbreviated application" referred to in your letter. Geneva has not launched its tablet product. We do not have information about the status of any patent certifications in that ANDA. Those certifications, and the course of litigation, or the lack of litigation, between Geneva and Abbott concerning any patents are, necessarily, the reason for your office's not notifying Zenith that its ANDA "may be considered."

We cannot know the exact basis for your office's position, because the information in question is apparently proprietary to Geneva. In a telephone call between a member of your office and Mr. Banks of Zenith Goldline, no information was provided to explain the continued delay in the processing of the Zenith ANDA. However, the trade press report states:

Geneva's settlement with the Federal Trade Commission regarding generic terazosin (*Hytrin*) requires the company to surrender its rights to 180-day exclusivity for a generic version of terazosin tablets.

If this report is correct, whatever technical or legal basis your office has had for deferring action on the Zenith ANDA appears no longer to exist. Therefore, please advise Zenith immediately that its ANDA "may be considered" for final approval and that your office will accept, and expeditiously act on, an amendment requesting final approval when it is submitted.

I would greatly appreciate your prompt response to our request. Thank you for your attention.

Sincerely yours,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Patricia Jaworski / for

Eric M. Mittleberg, Ph.D.
Vice President
Scientific Affairs/Technical Operations

Attachment

EMM: dj



DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, 314 & 601)</i>	Form Approved : OMB No. 0910-0338 Expiration Date: April 30, 2000 See OMB Statement on page 2.
	FOR FDA USE ONLY
	APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Zenith Goldline Pharmaceuticals, Inc.	DATE OF SUBMISSION MAR 24 2000
TELEPHONE NO. (Include Area Code) (201) 767-1700 ext. 323	FACSIMILE (FAX) Number (Include Area Code) (201) 767-3804
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 140 Legrand Ave Northvale, NJ 07647	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 74-530	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) TERAZOSIN HYDROCHLORIDE	PROPRIETARY NAME (trade name) IF ANY
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) (RS)-Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetra-hydro-2-furanyl)carbonyl]-, monohydrochloride, dihydrate	CODE NAME (If any)
DOSAGE FORM: Tablets	STRENGTHS: 1mg, 2mg, 5mg, 10mg
ROUTE OF ADMINISTRATION: Oral	
(PROPOSED) INDICATION(S) FOR USE: Antihypertensive	

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input checked="" type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)	
<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)	

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug Hytrin® Tablets Holder of Approved Application Abbott Laboratories

TYPE OF SUBMISSION (check one)			
<input type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION	
<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT	<input type="checkbox"/> SUPAC SUPPLEMENT
<input type="checkbox"/> EFFICACY SUPPLEMENT	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input checked="" type="checkbox"/> OTHER

REASON FOR SUBMISSION Letter to Gary Buehler

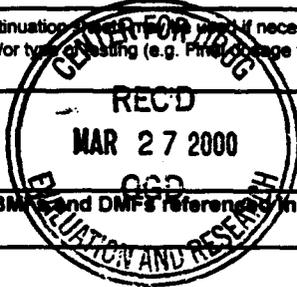
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED <u>1</u>	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
--------------------------------------	---

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheet if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMIs, and DMFs referenced in the current application)



This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
<input type="checkbox"/>	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
<input type="checkbox"/>	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (k) (3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input checked="" type="checkbox"/>	19. OTHER (Specify) Letter to Gary Buehler

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT

TYPED NAME AND TITLE Patricia Jaworski, Sr. Manager of Regulatory Affairs (New Products)

MAR 24 2000

ADDRESS (Street, City, State, and ZIP Code)
140 Legrand Ave Northvale, NJ 07647

Telephone Number
(201) 767-1700 ext. 323

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.



Zenith Goldline
P H A R M A C E U T I C A L S

Regulatory Affairs

FEB 9 2000

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FA
TELEPHONE AMENDMENT
7/1

TELEPHONE AMENDMENT- Labeling

RE: ANDA 74-530 – Terazosin HCl Tablets, 1 mg, 2 mg, 5 mg and 10 mg

Dear Mr. Sporn:

Reference is made to our pending, tentatively-approved Abbreviated New Drug Application for Terazosin HCl Tablets, 1 mg, 2 mg, 5 mg and 10 mg. Further reference is made to the Agency's telephone communications of January 24, January 27 and February 1, 2000.

As requested, we have revised the "How Supplied" section of our package insert labeling to include the company logo, "Z", as part of the product description. Please refer to Exhibit 1, in which we have provided six copies of the final printed package insert in each of the Archival and Review Copies of this amendment. To facilitate review, and in accordance with 21 CFR Part 314.94(a)(8)(iv), Exhibit 1 also includes a side-by-side comparison of the newly revised package insert versus the last submitted version, with all differences annotated and explained. Please be assured that the only difference in this revision is that specified for the inclusion of the "Z" logo in the product description of the "How Supplied" section.

Zenith Goldline Pharmaceuticals, Inc., has made a concerted effort to ensure that this response is complete, and that the labeling contained herein is satisfactory. Should the Office of Generic Drugs have any questions or require additional information, please contact our office at (201)767-1700, ext. 323/331.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.


Patricia Jaworski
Manager, Regulatory Affairs
(New Products)



Attachments

K:\Reg\2000 Amendments\Terazosin Tablets\Tel Amend Feb00.doc

140 Legrand Ave., Northvale, New Jersey 07647 • (201) 767-1700 (800) 387-0133 Fax (201) 767-3804

Miami, FL • Walton, KY • Cidra, P.R. • St. Croix, U.S. V.I.



Zenith Goldline

PHARMACEUTICALS

Regulatory Affairs

JAN 14 2000

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

N/FA

FAX AMENDMENT

Re: **ANDA 74-530**
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

Dear Mr. Sporn:

Reference is made to our pending, tentatively-approved abbreviated new drug application for Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg. At this time we are responding to the fax deficiencies noted in the agency's facsimile correspondence dated December 27, 1999 (copy attached). We understand that our response will be considered a Fax Amendment.

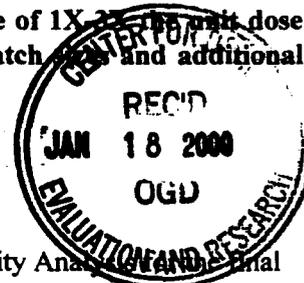
With regard to the agency's comments relating to our tentatively approved application, we are providing the following information and supportive data. The deficiencies are restated below in bold print, followed by our responses.

Comment:

- 1. In accordance with current policy, please provide a commitment to perform Blend Uniformity Analysis for the final granulation (all label claims) of all future production batches. We recommend a mean of 90.0% to 110.0% (% RSD \leq 5.0) and sample size of 1X 25 mg unit dose weight. A minimum of six samples is recommended for the smallest batch size and additional samples for larger batch sizes.**

Response:

- Zenith Goldline Pharmaceuticals, Inc. commits to performing Blend Uniformity Analysis for the final granulation of all future production batches of Terazosin HCl Tablets, 1 mg, 2 mg, 5 mg and 10 mg. As recommended by the Agency, Zenith Goldline has revised its drug product in-process blend



140 Legrand Ave., Northvale, New Jersey 07647 • (201) 767-1700 (800) 387-0133 Fax (201) 767-3804

Miami, FL • Walton, KY • Cidra, P.R. • St. Croix, U.S. V.I.

uniformity specification to 90.0%-110.0% (mean) with an RSD of NMT 5%. The revised blend specifications for all four strengths are presented in Exhibit 1 of this amendment. According to Zenith Goldline's Standard Operating Procedures (SOPs) on blend sampling, a total of thirty samples are taken from the blender during validation and routine manufacture of batches. Also, attached as Exhibit 2 is an addendum to page 566 of our original application, in which we have included blend testing.

Comment:

2. Please provide dissolution profiles for each label claim comparing the tablets with the original embossing (e.g. "Z4350" on one side and "1" on the other side) versus the revised debossing (∇over Δ on the upper half and 4350 on the lower on one side, and 1 on the other).

Response:

2. Zenith Goldline Pharmaceuticals respectfully asks that the Agency withdraw response #3, of our Minor Amendment dated November 9, 1999. At this time, Zenith Goldline Pharmaceuticals wishes to withdraw master formula/standard operating instructions and requests that our pending application be approved with the submitted in our original application:

Zenith Goldline Pharmaceuticals confirms that there have been no changes made to the application with regard to manufacturing, since the date of tentative approval (August 14, 1998).

Comment:

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with current cGMP's at the time of approval. We will request an evaluation from the Division of Manufacturing and Product Quality at the appropriate time.

Response:

1. Zenith Goldline Pharmaceuticals acknowledges the agency's comment that the firms referenced in the application relative to the manufacture and testing of the product must be in compliance with current cGMP's at the time of approval.

Comment:

2. Please define the pharmaceutical function of each inactive ingredient in the drug product formulation.

Response:

2. The following table defines the pharmaceutical function of each inactive ingredient in the drug product formulation for Terazosin HCl Tablets, 1 mg, 2 mg, 5 mg and 10 mg.

Inactive Ingredient	Function
I Lactose Monohydrate, NF	Filler, Diluent
I Starch, NF	Binder, Diluent, and Disintegrant
I Crospovidone, NF	Disintegrant
I Colloidal Silicon Dioxide, NF	Glidant
I Talc, USP	Glidant
I Magnesium Stearate, NF	Lubricant
I Pink Titanium Lake Blend	Colorant
I Pigment Blend Yellow	Colorant
I FD&C Blue #2 Aluminum Lake	Colorant

I Used in the 2 mg formulation.

II Used in the 5 mg formulation.

III Used in the 10 mg formulation.

This completes our response to the Agency's fax correspondence of December 27, 1999, covering CMC deficiencies.

Zenith Goldline Pharmaceuticals has made every effort to ensure that this response is complete and that the information contained herein is satisfactory. Should the Office of Generic Drugs have any questions or require additional information, please contact our office at (201) 767-1700 x 239.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director, Global Regulatory Affairs





Zenith Goldline
P H A R M A C E U T I C A L S

Regulatory Affairs

NOV 9 1999

ORIG AMENDMENT

N/A M

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

RE: ANDA #74-530
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

Dear Mr. Sporn:

Reference is made to Zenith Goldline's Abbreviated New Drug Application dated August 1, 1994 and the agency's tentative approval letter dated August 14, 1998 (copy attached).

The reference listed drug product upon which this application is based is subject to a period of patent protection which expires on April 29, 2013, (Patent No. 5,504,207). Pursuant to Section 505(j)(5)(B)(iii) of the Act, Zenith Goldline acknowledges that final approval of this Abbreviated New Drug Application will be made effective immediately unless an action is brought before the expiration of forty-five days from the date the notice provided under paragraph (2) (B) (I) is received.

We also acknowledge that FDA has been notified that Zenith Goldline Pharmaceuticals has complied with the requirements of Section 505(j)(2)(B) of the Act by providing the required notice to each patent holder, and that no action for patent infringement was brought against Zenith Goldline within the statutory forty-five day period.

Zenith Goldline recognizes that a previous abbreviated application for Terazosin Hydrochloride Tablets, 1 mg (base), 2 mg (base), 5 mg (base) and 10 mg (base), with a paragraph IV certification, has been submitted. Accordingly, we understand that our application will be eligible for final approval beginning on the date that is one hundred and eighty days after the date the agency receives notice of the first commercial marketing of the drug under the previous application, or the date of a court decision described under section 505(j)(5)(B)(iv), whichever is earlier.

140 Legrand Ave., Northvale, New Jersey 07647 • (201) 767-1700 (800) 387-0133 Fax (201) 767-3804

Miami, FL • Walton, KY • Cidra, P.R. • St. Croix, U.S. VI.

N/A M
11-11-99

Zenith Goldline acknowledges that final approval of our Abbreviated New Drug Application will not be made effective until one hundred and eighty days after July 1, 1999, the date of the decision of a court holding the patent which is the subject of the certification to be invalid or not infringed (See Exhibit 1).

The tentative approval letter sets forth the requirement to report all changes to the provisions of this application at least 60, but no more than 90 days prior to final approval. In accordance with this requirement, Zenith Goldline hereby submits this minor amendment to advise the agency of updated information and changes pertinent to the labeling, chemistry, manufacturing and control provisions of our application.

In our effort to address all open issues related to this application, and obtain final approval, we present the following:

Comment:

“Your amendment, which must be submitted as least 60, but not more than 90 days prior to final approval must then provide:

1. updated information related to labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or
2. a statement that no such changes have been made to the application since the date of tentative approval.”

Response:

1) **With Regard to Labeling:**

At this time, we are amending our application by revising our container labels, package insert labeling and patient's information leaflet. To facilitate review of the submission, we have provided a side-by-side comparison of the container labels, insert labeling and patient's information leaflet proposed in this amendment versus the last submitted labeling, with all differences annotated and explained. These can be found accompanying the final printed container labels, package insert labeling and patient's information leaflet in Exhibit 2 of this amendment.

2) **With Regard to Chemistry:**

On April 19, 1997, Zenith Goldline received a telephone communication from the agency requesting that we submit a commitment to perform blend assay testing on a routine basis considering the low dose of this drug product. Zenith Goldline responded to the agency's request via Telephone Amendment on April 24, 1997 and committed to continue blend testing. Presented as Exhibit 3 are the revised blend specifications for all four dosage strengths of Terazosin HCl Tablets.



3) **With Regard to Manufacturing:**

The commercial scale standard operating instructions for the 1 mg, 2 mg, 5 mg and 10 mg dosage strengths were revised to incorporate the following:

- reduction in batch size from units to units,
- new company logo (debossing),
- equipment size and mixing times changed to reflect reduction in batch size,
- deletion of statement, "Upon completion of process validation, the blend test may be discontinued," and
- provision made to use vacuum cleaner during compression.

These changes are reflected in SOI #S-4350-2A-2A (1 mg), #S-4351-2A-2A (2 mg), #S-4352-2A-2A (5 mg), and #S-4353-2A-2A (10 mg) and are included as Exhibit 4 of this amendment. These standard operating instructions will be used to manufacture the first validation batch of each dosage strength.

Additionally, in support of the revision, Zenith Goldline has included updated finished product and stability specifications referencing the change in company logo in the product description. The revised finished product and stability specifications are presented as Exhibit 5.

These data demonstrate that the minor changes in the commercial scale process will have no adverse effect on the quality and release of the drug product. Finally, please be advised that all changes referenced in our standard operating instructions will also be appropriately addressed in our process validation reports and made available for district review and approval.

4) **With Regard to Controls:**

On June 24, 1999, Zenith Goldline submitted to the agency a global supplement to include our manufacturing facility, Zenith Laboratories Caribe, Inc. as an alternative testing laboratory. This laboratory site will be used to conduct all testing related to raw material, finished product, and testing of stability samples.

Zenith Goldline Pharmaceuticals has made a concerted effort to ensure that this application contains all of the information that the Office of Generic Drugs may require. Should you have any questions or require some additional information, please contact our office at your convenience (201) 767-1700 x. 239.

With Best Regards,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross, Pharm. D.
Director, Global Regulatory Affairs

Attachments





Zenith Goldline
P H A R M A C E U T I C A L S

June 29, 1998

ORIG AMENDMENT

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

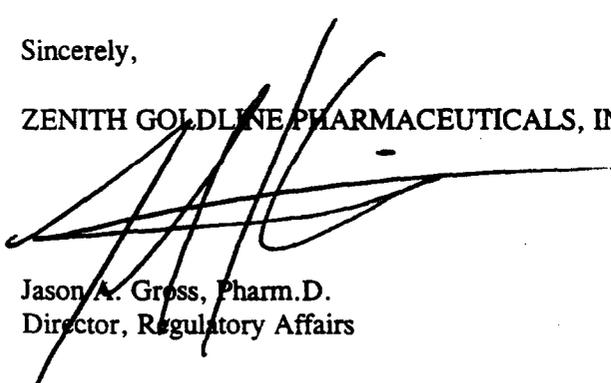
Re: Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg
ANDA 74-530

Dear Mr. Sporn:

Reference is made to our above ANDA for Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg which was filed on August 1, 1994, our patent amendment dated April 9, 1998 and the June 15, 1998 telephone conversation between Dr. Jason Gross of Zenith Goldline and Jerry Phillips and Peter Rickman of the Agency. Reference is also made to the Agency's Deficiency Letter dated June 24, 1998 (copy attached) in which you request that we provide Documentation of Notification/Receipt of Notice as specified in 21 CFR 314.95. In response to this request, Zenith Goldline Laboratories, Inc. certifies that notification of the form specified in 21 CFR 314.95 (c) was provided to Abbott Laboratories, the owner of the challenged patents and holder of the approved application for the reference listed drug. Additionally, we have attached a Receipt for Certified Mail indicating that Abbott accepted our notice on April 15, 1998. Because no legal action was taken by Abbott Laboratories within the 45-day period specified in section 505(j)(4)(B)(iii) of the Act, the Agency may presume this notice to be complete and sufficient. In accordance with the instructions of your June 24, 1998 letter, we have labeled this response as a MINOR AMENDMENT.

Sincerely,

ZENITH GOLDLINE PHARMACEUTICALS, INC.


Jason A. Gross, Pharm.D.
Director, Regulatory Affairs

RECEIVED
JUN 30 1998
GENERIC DRUGS

Madhusudan
88-1-1

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583

Miami, FL • Walton, KY • Cidra, P.R. • St. Croix, U.S. V.I.

310-2
74530



Zenith Goldline

PHARMACEUTICALS

June 3, 1998

Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N/AA

Re: Global - Special Supplement - Changes Being Affected- PAC-ATLS
For: Alternate Testing Laboratory Site
The submission is relevant to the list of Abbreviated New Drug Applications referenced in Attachment 1

Dear Dr. Sporn:

As provided under 21 CFR 314.70, Zenith Goldline Pharmaceuticals hereby submits a global supplement to include [CFN 1021259] as an alternative testing laboratory for fifty two approved abbreviated new drug applications [Attachment 1]. This laboratory will be used to conduct all testing related to raw material, finished product, and testing of stability samples. No biological testing will be performed at the new laboratory site for the products, which are the subject of this filing.

Changes in an approved application to allow for the use of a different facility or establishment, including a different contracting laboratory, normally require FDA approval before the change is made [21CFR 314.70(b)]. FDA regulations at 21 CFR 314.70(a) provide that applications may make changes to an approved application in accordance with a guidance, notice, or regulations published in the federal register that provides for a less burdensome notification of the change. The PAC-ATLS, Post approval Changes - dated April 1998, provides guidance on a less burdensome approach to providing notice within the meaning of 21 CFR 314.70(a), as such Zenith Goldline is submitting the addition of an alternative testing site as a changes being effected supplement, as directed in the aforementioned guidance.

The test methods used by [redacted] will be the same test methods as those approved in each affected application. Zenith Goldline has audited this laboratory and find they have the capability of conducting the intended testing. They have had a satisfactory cGMP inspection within the last two years as the last inspection was conducted February 9, and February 13, 1998. No FDA483 was issued. Also you will find for your information [redacted] SOP Index, Last FDA Inspection report and equipment list. [Attachment 2].

As stipulated in the PAC-ATLS guidance, prior to submitting this supplement Zenith Goldline has assured that [redacted] are capable of conducting the intended testing and the information to support this conclusion such as comparative data, their cGMP history and appropriate SOPs are available for FDA inspection upon request. Attachment 3, contains a statement from Zenith Goldline's Director of Assurance Department that [redacted] was audited and the results of this audit demonstrate that the laboratory is capable of conducting the intended testing.

RECEIVED
JUN 12 1998

GENERIC DRUGS

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583

Miami, FL • Walton, KY • Cidra, P.R. • St. Croix, U.S. V.I.

June 3, 1998
Global Supplement
Page 2

Proposed Alternative Analytical Testing Facility:

Should you have any questions, please contact my office at your convenience.

With Best Regards,

ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross for

Jason A. Gross, Pharm.D.
Director, State, Federal and
International Regulatory Affairs

Enclosures.





Zenith Goldline
PHARMACEUTICALS

Regulatory Affairs

June 16, 1998

Douglas L. Sporn, Director
Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Request for a meeting with Office of Generic Drugs and FDA Council
ANDA 74-530 - Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg, and 10 mg

Dear Mr. Sporn:

Reference is made to our April 9, 1998 submission. Accordingly, in response to the Agency's request, Zenith amended the referenced application with the required patent certifications for U.S. Patent Nos. 5,504,207 and 5,412,095. The attached Paragraph IV certifications state that both patents are unenforceable against Zenith and will not be infringed by the manufacturer, use or sale of the terazosin hydrochloride product for which Zenith's ANDA 74-530 is submitted. These certifications are based on a Covenant Not to Sue between Zenith Goldline Pharmaceuticals, Inc. and Abbott Laboratories, Inc. that was included with our submission.

Reference is also made to the June 15, 1998 telephone conversation between Jerry Phillips, Peter Rickman and myself.

During the referenced telephone conversation, Mr. Phillips informed Zenith Goldline that the submitted covenant fails to satisfy the provisions of 21 CFR 314.95. Mr. Phillips specified that Zenith Goldline would either need to supply a letter from Abbott that stipulates they do not intend to sue Zenith Goldline or notify Abbott that Zenith Goldline has filed an application and wait 45 days. When Zenith Goldline asked Mr. Phillips why the covenant is not the same as receiving a correspondence from Abbott that they do not intend to sue Zenith Goldline, he stipulated the bases for this decision was that he did not know if the covenant was acceptable to Abbott. Mr. Phillips was informed that the covenant is signed by the President of Abbott, there have been numerous press releases about this settlement and is welcome to call Abbott to verify its authenticity. Based on this conversation, Zenith Goldline would like to request a meeting with the office of generic drugs

140 Legrand Ave., Northvale, New Jersey 07647 • (201) 767-1700 (800) 387-0133 Fax (201) 784-1719

Miami, FL • Walton, KY • Cidra, P.R. • St. Croix, U.S. V.I.

Mr. Doug Sporn
June 16, 1998
Page 2

and their legal council to fully clarify how the covenant fails to supply the Office with enough information to conclude that Abbott has agreed not to sue Zenith Goldline with respect to our certification.

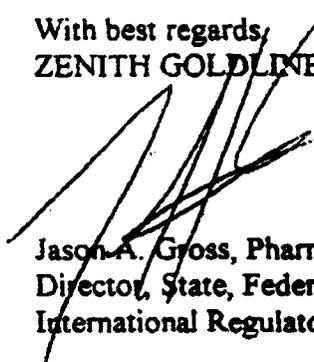
It is Zenith Goldline contention that all provisions of 21 CFR 314.95 have been satisfied and thus our application should be approved. As provided by 21 CFR 314.95(b), Abbott was notified of the existence of the application. This may be affirmed by the FDA reviewing Zenith Laboratories, Inc. vs. Abbott Laboratories, Inc. Civil Action No. 96 Civ 1661, pending in the United States District Court for the District of New Jersey. 21 CFR 314.95(e) has been satisfied in that on March 31, 1998, the executed date of the covenant Abbott acknowledges the patents and stipulates they agree not to enter into a law suit regarding the referenced patents. The existence of the covenant further substantiates that Abbott was indeed notified. As Abbott and Zenith Goldline have entered into a covenant the provisions of 21 CFR 314.95(f) became irrelevant. However, Zenith Goldline would agree to using March 31, 1998 as the start date for the 45 day clock. 21 CFR 314.95(e) further allows the Office to use its desecration in determining what satisfies the requirements of documentation.

Additionally, we certify that no significant changes in the conditions outlined in our abbreviated new drug application for Terazosin Hydrochloride Tablets (74-530) have been made. We believe that the information provided with this minor amendment clears the way for final approval of our ANDA.

We request and appreciate the Agency's timely consideration of this matter.

Should you have any questions, please contact my office at your convenience.

With best regards,
ZENITH GOLDLINE PHARMACEUTICALS, INC.


Jason A. Gross, Pharm.D.
Director, State, Federal and
International Regulatory Affairs



Zenith Goldline
 PHARMACEUTICALS

April 9, 1998

Douglas L. Sporn, Director
 Office of Generic Drugs
 CDER, FDA
 Document Control Room
 Metro Park North II
 7500 Standish Place, Room 150
 Rockville, MD 20855-2773

ORIG AMENDMENT
JH

MINOR AMENDMENT

RE: Terazosin HCl Tablets, 1 mg, 2 mg, 5 mg, and 10 mg
 ANDA 74-530
Patent Certifications

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application for Terazosin HCl Tablets, ANDA 74-530, and the July 8, 1997, Agency Correspondence which specified certifications that were required for each patent filed. Reference is also made to our correspondence of February 27, 1998, which described the status of the court case, and requested the Agency's assistance in obtaining an expeditious approval upon its settlement. (Copies of these letters are attached.)

Accordingly, in response to the Agency's request Zenith is amending the referenced application with the required patent certifications for U.S. Patent Nos. 5,504,207 and 5,412,095. The attached Paragraph IV certifications state that both patents are unenforceable against Zenith and will not be infringed by the manufacture, use or sale of the terazosin hydrochloride product for which Zenith's ANDA 74-530 is submitted. These certifications are based on a Covenant Not to Sue (copy attached) between Zenith Goldline Pharmaceuticals, Inc. and Abbott Laboratories.

In order to satisfy the provisions of 21 CFR 314.95, a copy of the aforementioned Covenant is attached, as the Covenant demonstrates that Abbott Laboratories has been notified of the referenced filing. As the Covenant stipulates, Abbott has granted to Zenith a Covenant Not to Sue, and accordingly, the provisions of notification as provided under 21 CFR 314.95 have been satisfied. As such, the provisions of 21 CFR 314.95(f) are not applicable, and thus we request that approval of our Terazosin HCl Tablets ANDA be made effective immediately.

Additionally, we certify that no significant changes in the conditions outlined in our abbreviated new drug application for Terazosin HCl Tablets (74-530) have been made. We believe that the information provided with this minor amendment clears the way for final approval of our ANDA.

We request and appreciate the Agency's timely consideration of this matter.

With Best Regards,
 ZENITH GOLDLINE PHARMACEUTICALS, INC.

Jason A. Gross

Jason A. Gross, Pharm.D.
 Director, Regulatory Affairs

RECEIVED

APR 13 1998

GENERIC DRUGS

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583

Miami • Ft. Lauderdale • Cidra, P.R. • St. Croix, U.S. V.I. • Shreveport • Mason • Syosset

Madame
 4-77-98



Zenith Goldline
P H A R M A C E U T I C A L S

February 27, 1998

Mr. Douglas L. Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metropark North II
7500 Standish Place
Rockville, MD 20855

Re: Terazosin Hydrochloride Tablets, ANDA 74-530

Dear Mr. Sporn:

Reference is made to your letter dated July 8, 1997, stating that our Abbreviated New Drug Application for Terazosin Hydrochloride Tablets is deficient and, therefore, not approvable based solely on Zenith's failure to amend its application to provide patent certifications for two United States patents owned by Abbott Laboratories; namely, U.S. Patents Nos. 5,504,207 ("the '207 patent") and 5,412,095 ("the '095 patent"); each expiring on April 29, 2013.

It is Zenith's position that both of such patents have been improperly listed by Abbott in the Orange Book, and, accordingly, Zenith should have no obligation to file certifications with respect thereto. In an action filed by Zenith against Abbott in the United States District Court for the District of New Jersey (No. 96-1661), Zenith has asked the district court to order Abbott to delist its '207 and '095 patents from the Orange Book, and Zenith's position on this listing issue is presently on review at the United States Court of Appeals for the Federal Circuit.

It is Zenith's hope that a decision may be rendered within the next two to six months by the Federal Circuit that will establish that Abbott's patent listings are indeed improper and will result in an order directing Abbott to delist such patents.

Given the substance of your correspondence, it is Zenith's understanding that, should the patents be delisted, there would be no need to certify against such patents and no impediment would exist preventing final approval of Zenith's ANDA. In anticipation of the courts order for Abbott to delist the '207 and '095 patents, we are writing to you now, to alert you to this pending court action so that a plan of action may be developed to expedite final approval of Zenith's ANDA upon the delisting of Abbott's patents.

We look forward to hearing from you or someone on your staff regarding how we may be able to facilitate the approval process, so that we can immediately bring our product to market should we receive a favorable court ruling.

We look forward to hearing from you with regard to the foregoing.

With best regards,

ZENITH GOLDLINE PHARMACEUTICALS

Jason A. Gross, Pharm.D.
Director, Regulatory Affairs

JAG:go

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583

Miami • Ft. Lauderdale • Cidra, P.R. • St. Croix, U.S. V.I. • Shreveport • Mason • Syosset



Zenith Goldline
P H A R M A C E U T I C A L S

April 24, 1997

NDA ORIG AMENDMENT

Joe Buccine
Project Manager, Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

N/A M

RE: Terazosin HCl Tablets, 1 mg, 2 mg, 5 mg and 10 mg
ANDA 74-530,

TELEPHONE AMENDMENT

Dear Mr. Buccine:

Reference is made to the April 18, 1997 telephone conversation between Ms. Karen Rocco of Zenith Goldline Pharmaceuticals, Inc. and Dr. Alan Rudman, at the Office of Generic Drugs. The Agency requested that we submit a commitment to perform blend assay testing on a routine basis considering the low dose of this drug product. We hereby agree to continue blend testing on a routine basis. When sufficient data becomes available, we will supplement our application accordingly.

We understand that completes all outstanding issues surrounding the approval of this application, and now look forward to its approval. Thank you for your attention to this matter.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.

Janice McNeill,
Regulatory Associate

jm\k:reg\terazosin\faxamend.doc

RECEIVED

APR 25 1997

GENERIC DRUGS

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583

Miami • Ft. Lauderdale • Cidra, P.R. • St. Croix, U.S. V.I. • Shreveport • Mason • Syosset



Zenith Goldline
P H A R M A C E U T I C A L S

April 24, 1997

Mr. Joseph Buccine
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

NC

CORRESPONDENCE

RE: Terazosin Hydrochloride Tablets
1mg, 2mg, 5mg, and 10mg
ANDA 74-530

Dear Mr. Buccine:

As requested by Joseph Buccine, Office of Generic Drugs Project Manager, on April 17, 1997, we are providing patent certification information regarding the ANDA for Terazosin hydrochloride tablets filed by Zenith Goldline Pharmaceuticals, Inc. ("Zenith"), filed on or about August 1, 1994. It is our present understanding that issues of patent certification are all that remain for resolution in connection with Zenith's ANDA, and it is hoped that the information provided herein will permit such issues to be resolved.

The patents currently listed in the Orange Book as applicable to HYTRIN® (terazosin hydrochloride dihydrate) oral tablets are as follows: U.S. Patent No. 4,026,894 ("the '894 patent"); U.S. Patent No. 4,112,097 ("the '097 patent"); U.S. Patent No. 4,251,532 ("the '532 patent"); U.S. Patent No. 5,294,615 ("the '615 patent"); U.S. Patent No. 5,212,176 ("the '176 patent"); U.S. Patent No. 5,412,095 ("the '095 patent"); and U.S. Patent No. 5,504,207 ("the '207 patent"). Each of these patents will be addressed separately herein below with regard to the issue of certification.

The '894 Patent

Zenith's ANDA included a "paragraph II" certification regarding the '894 patent, noting that it had expired. Accordingly, no further information regarding this patent should be required.

RECEIVED

The '097 Patent

APR 25 1997

Zenith's ANDA included a "paragraph III" certification as to the '097 patent, noting that Zenith only sought approval to market its generic version of terazosin hydrochloride tablets upon the scheduled expiration of the '097 patent on September 5, 1995. Although the term the

GENERIC DRUGS

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583

Miami • Ft. Lauderdale • Cidra, P.R. • St. Croix, U.S. V.I. • Shreveport • Mason • Syosset

'097 patent was extended under GATT, the extended term has expired as well, and accordingly, no further patent certification information regarding this patent should be required.

The '532 Patent

Zenith's ANDA included a "paragraph IV" certification with respect to the '532 patent and, by letter dated September 9, 1994 (copy enclosed), Abbott was advised as to the reasons why Zenith's proposed generic terazosin hydrochloride does not infringe such patent. By letter dated September 15, 1994 (a copy of which is enclosed herewith), Abbott acknowledged receipt of Zenith's letter dated September 9, 1994 and requested samples of Zenith's terazosin hydrochloride product for testing, which samples were provided thereafter. Abbott has never contested Zenith's assertion of noninfringement with regard to the '532 patent, and Zenith hereby reiterates its "paragraph IV" certification of noninfringement with respect thereto.

The '615 Patent

It is Zenith's position that the '615 patent has been improperly listed by Abbott because such patent does not cover Abbott's HYTRIN® product or a method of using HYTRIN®. In any event, it also has been determined that, with respect to Zenith's ANDA, the '615 patent was not timely filed, and therefore, Zenith has no obligation to file any certification with respect thereto. That this is the case was confirmed to me in a telephone discussion with Ms. Cecelia Parisi on April 3, 1996.

The '176 Patent

It is Zenith's position that the '176 patent has been improperly listed by Abbott because such patent does not cover Abbott's HYTRIN® product or a method of using HYTRIN®. In any event, as in the case of the '615 patent, it also has been determined that, with respect to Zenith's ANDA, the '176 patent was not timely filed, and therefore, Zenith has no obligation to file any certification with respect thereto. That this is the case was also confirmed to me in a telephone discussion with Ms. Cecelia Parisi on April 3, 1996.

The '095 Patent

It is Zenith's position that the '095 patent has been improperly listed by Abbott because such patent does not cover Abbott's HYTRIN® product or a method of using HYTRIN®. The impropriety of Abbott's listing of this patent is the subject of a complaint filed by Zenith against Abbott in the United States District Court for the District of New Jersey (Civil Action No. 96-1991 (DRD)), in which Zenith has asked the Court to order Abbott to delist the '095 patent from the Orange Book.



The '207 Patent

It is Zenith's position that the '207 patent has been improperly listed by Abbott because such patent does not cover Abbott's HYTRIN® product or a method of using HYTRIN®. The impropriety of Abbott's listing of this patent is also the subject of the complaint filed by Zenith against Abbott in the United States District Court for the District of New Jersey in which Zenith has asked the Court to order Abbott to delist the '027 patent from the Orange Book

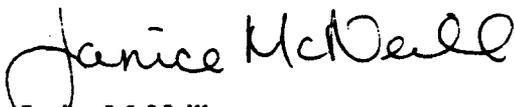
* * *

To summarize, it is Zenith's position that although Abbott's '095 and '207 patents are listed in the Orange Book, since such patents were improperly listed, Zenith should not be required to file any patent certifications with respect thereto. In this regard, and as noted above, Zenith's position with regard to the impropriety of Abbott's listing of these patents in the Orange Book is, in part, the subject of a complaint filed by Zenith against Abbott in the United States District Court for the District of New Jersey. If it is FDA's position that final approval of Zenith's ANDA cannot be granted unless Zenith files appropriate certifications with respect to the '095 and '207 patents, or unless such patents are delisted by Abbott, then Zenith respectfully requests FDA to issue a letter to Zenith so stating and further indicating that issues of patent certification with respect to these two patents are all that stand in the way of Zenith's final approval. Immediately upon receipt of such a letter, it would be Zenith's intention to approach the Court and seek expedited consideration of Zenith's request that Abbott be ordered to delist the patents in question.

Should you require any further information from us to help you in your consideration of this matter, please do not hesitate to contact me at any time.

Sincerely,

ZENITH GOLDLINE PHARMACEUTICALS, INC.


Janice McNeill
Regulatory Associate

Enclosures (2)
jm\k:\veg\terazo\patent.doc





Zenith Goldline
P H A R M A C E U T I C A L S .

April 15, 1997

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

AMENDMENT

N/AM

RE: Terazosin HCl Tablets, 1 mg, 2 mg, 5 mg and 10 mg
ANDA 74-530, MINOR TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to the March 4, 1997 telephone conversation between Ms. Joan Janulis of Zenith Goldline Pharmaceuticals, Inc. and Mr. Joseph Buccini, Project Manager, OGD. In that conversation, the Agency requested that a revision of our raw material specification be made to include a limit of % for each individual impurity other than

It was also requested that the limits for the corresponding impurities contained in our finished product release specifications be lowered to % and maintained at % in the stability specifications. We have agreed to implement these changes and on March 14, 1997 we received the Agency's verbal acceptance of the proposed limits from Mr. Buccini.

In response to the Agency's request, ZENITH GOLDLINE PHARMACEUTICALS, Inc. hereby submits this Minor Telephone Amendment which includes:

1. One copy of the revised raw material specifications form containing the requested % limit for each individual impurity other than
2. One copy of the associated method for determining chromatographic purity of the raw material which has been amended to include calculations for each individual impurity/degradant.

RECEIVED

APR 16 1997

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 461-7700 • (800) 631-1583

Miami • Ft. Lauderdale • Cidra, P.R. • St. Croix, U.S. V.I. • Shreveport • Mason • Syosset

Terazosin HCl Tablets, ANDA 74-530

April 15, 1997

page 2

3. One copy of the revised finished product specifications form (for each tablet strength) containing the requested % limit for each other individual impurity.
4. One copy of the stability specification (for each tablet strength) containing the accepted % limit for each other individual impurity.

We understand that completes all outstanding issues surrounding the approval of this application, and now look forward to its approval. Thank you for your attention to this matter.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.



Karen Rocco,
Associate Director, Regulatory Affairs

l:\kreg\terazosin\finanem.doc





Zenith Goldline
P H A R M A C E U T I C A L S

February 12, 1997

72
NDA ORIG AMENDMENT

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/A

RE: Terazosin HCl Tablets, 1 mg, 2 mg, 5 mg and 10 mg
ANDA 74-530, MINOR TELEPHONE AMENDMENT

Dear Sir/Madam:

Reference is made to the November 25, 1996 telephone conversation between myself and Ms. Carol Holquist from the Labeling Review Division, during which Ms. Holquist requested revision of our Patient Package Insert labeling for the subject product.

In response to Ms. Holquist's request, Zenith Goldline Pharmaceuticals Inc. hereby submits this Minor Telephone Amendment which includes twelve (12) final printed copies of our patient package insert labeling.

Additionally, Ms. Holquist requested a commitment from Zenith Goldline to update our container labels prior to product launch. The update is necessary in order to keep the "Manufactured by" statement consistent with the one that is currently contained in our package insert labeling. Please note that during the review process for this application, our firm was undergoing a transition in which all labeling was being updated to reflect the address of our Corporate headquarters in Ft. Lauderdale, FL. Consequently, the container labels submitted in the application referenced our Northvale, New Jersey address, while the package insert had been updated to reflect the Ft. Lauderdale address.

RECEIVED

FEB 13 1997

GENERIC DRUGS

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583

Miami • Ft. Lauderdale • Cidra, P.R. • St. Croix, U.S. V.I. • Shreveport • Mason • Syosset

Terazosin HCl Tablets, ANDA 74-530

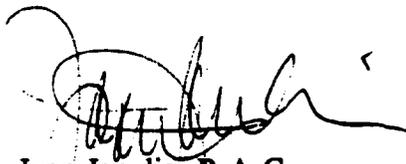
February 12, 1997

Page 2

Zenith Goldline recognizes the need to update our container labels to reference the Ft. Lauderdale address and will comply with this requirement prior to launching the product.

Thank you for your kind attention to this matter.

Sincerely,
Zenith Goldline Pharmaceuticals, Inc.



Joan Janulis, R.A.C.
Director, Regulatory Affairs





Zenith Goldline
PHARMACEUTICALS

January 8, 1997

Douglas L. Sporn
Director, Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA CRIS AMENDMENT
N/A

Terazosin Hydrochloride Tablets,
1 mg, 2 mg, 5 mg, and 10 mg
ANDA 74-530
MINOR AMENDMENT RESPONSE

RECEIVED

JAN 09 1997

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application for Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg. At this time we are responding to the deficiencies noted in the Agency's letter of November 8, 1996 (copy attached). We understand that our response will be considered a MINOR amendment. In reply to your observations, we are providing the following information and support documentation:

Comment:

1. The recent responses to Drug Master File by the holder have been reviewed and remain deficient. The holder has been notified.

Response:

Attachment 1 of this amendment includes a letter from _____ (agent for the drug substance manufacturer, _____) stating that _____ responded to the recent deficiencies cited in DMF on December 4, 1996.

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583

Miami • Ft. Lauderdale • Cidra, P.R. • St. Croix, U.S. V.I. • Shreveport • Mason • Syosset

Handwritten:
N/A
1-10-97

Comment:

2. Your Assay specification for the drug substance Terazosin Hydrochloride does not agree with the specification supplied by [redacted]. The Assay specification should be revised to [redacted] % as $C_{19}H_{25}N_5O_4 \cdot HCl$ (terazosin hydrochloride) on anhydrous basis.

Response:

As requested, Zenith Goldline has revised our Assay specification for Terazosin Hydrochloride from [redacted] % to [redacted] %, the same as that supplied by the drug substance manufacturer. The updated release specifications reflecting the revised Assay limits are provided in Attachment 2 of this amendment.

Additionally, in conjunction with the reduced impurity limits for finished product release and stability (requested in comments 3 and 4 of this amendment), we have reduced the impurity limits for the drug substance. The reduced limits incorporated into our revised drug substance specifications are as follows:

Chromatographic Impurity	Previous Limit	Revised Limit
[redacted]	%	%
Total Impurities/Degradants	%	%

These revised impurity specifications provide for a tiered approach in the assignment of impurity limits, with appropriate increases in the total impurities/degradants between the drug substance, finished product and stability specifications. This approach is illustrated in the summary following our response to Comment 4.

In addition to the revisions prompted by the Agency's comments, please be advised that Zenith Goldline has also incorporated changes with respect to our Residual Solvents test method and specifications. Specifically, we have developed and validated a new method to encompass an additional residual solvent, [redacted] not previously included in our specifications. Recently it came to our attention that the drug substance manufacturer, [redacted] uses [redacted] in the synthetic process for Terazosin Hydrochloride. This solvent is cited in [redacted] certificate of analysis as [redacted] and has a specified limit of 100 PPM. (A copy of the certificate of analysis included in our original application has been extracted and provided in Attachment 2 as reference.) In order to incorporate this additional solvent in our drug substance



release specifications we have developed and validated residual solvent method which incorporates testing for both the previously specified residual solvents,

and the new solvent, Our proposed test method, and the corresponding validation report are included in Attachment 2 for your review. Please note that our revised drug substance release specifications (also provided in Attachment 2) incorporate a limit of 100 PPM for the same as that established by

Furthermore, please be advised that although the a new test procedure has been implemented, the limits for the previously specified solvents remain unchanged.

We trust that you will find our validation report supportive of our proposed residual solvent method and specifications and apologize for any inconvenience this change may cause in your review.

Comment:

3. It is noted that the impurity level for does not exceed % and that the total impurities do not exceed % for the release of the four strengths of drug product. These levels should be reduced in your release specifications to NMT % for and NMT % for total impurities for total impurities for release of the four dosage strengths.

Response:

In accordance with the Agency's request, we have revised our finished product release specifications for all four dosage strengths to reduce the level of to NMT % and the level of total impurities to NMT %. Please refer to Attachment 3 for our updated release specifications.

Comment:

4. It is noted also that the impurity level in your accelerated stability studies for does not exceed % and that total impurities do not exceed % for the four strengths of the drug product. These levels should be reduced in your stability protocol specifications to NMT % for and NMT % for total impurities.



Response:

Zenith Goldline has reduced the limit for _____ from NMT % to NMT % as requested. This revised limit is reflected in our amended stability protocol specifications included in Attachment 4 of this amendment.

With respect to the reduction of the total impurities level, please note that our 24 month stability data indicate an increase of approximately % in total impurities/degradants as summarized in the following table:

ANDA Batch	Total Impurities/ Degradants	Total Impurities/ Degradant Increase
ND-190 (1 mg)		
ND 192 (2 mg)		
ND 193 (5 mg)		
ND 194 (10 mg)		

Based on the above data accrued to date, Zenith Goldline proposes to revise the limit of total impurities/degradants from NMT % to NMT % rather than the Agency's recommended limit of NMT %. This modification in the total impurities/degradant limit was discussed during a teleconference with Agency representatives (Dr. A. Mueller, Dr. P. Schwartz and Mr. J. Buccine) on December 19, 1996. It is our opinion that the proposed level of NMT % accurately reflects the approximate increase of impurities expected during the shelf life of our drug product. Accordingly, our stability protocol specifications provided in Attachment 4 include the proposed limit of NMT % for total impurities/degradants.

In summary, our revised release specifications for the drug substance, finished product and stability stages reflect the following reduction in impurity limits:

CHROMATOGRAPHIC PURITY	DRUG SUBSTANCE		FINISHED PRODUCT		STABILITY	
	Previous	Revised	Previous	Revised	Previous	Revised
Total Impurities/Degradants						



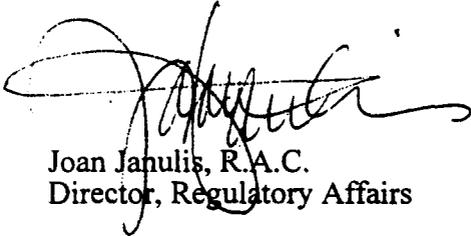
*Terazosin Hydrochloride Tablets,
1 mg, 2 mg, 5 mg and 10 mg
ANDA 74-530*

*January 8, 1997
MINOR AMENDMENT
RESPONSE
Page 5*

We are confident that our revised release specifications are appropriately set and will ensure the quality and purity of our proposed drug product.

This completes our response to the minor deficiency letter dated November 8, 1996. We trust that all outstanding deficiencies have been adequately addressed and look forward to the approval of our Abbreviated New Drug Application.

Sincerely,
ZENITH GOLDLINE PHARMACEUTICALS, INC.



Joan Janulis, R.A.C.
Director, Regulatory Affairs





Zenith Goldline
P H A R M A C E U T I C A L S

ORIGINAL

NDA ORIG AMENDMENT

August 29, 1996

Mr. Douglas L. Sporn
Director
Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED

SEP 03 1996

GENERIC DRUGS

MINOR AMENDMENT

RE: **Terazosin Hydrochloride Tablets**
1 mg, 2 mg, 5 mg, and 10 mg
ANDA 74-530

Dear Mr. Sporn:

Reference is made to our pending abbreviated new drug application for Terazosin Hydrochloride Tablets. Reference is also made to the Agency's letter dated June 24, 1996 which noted certain deficiencies resulting from the review of our April 25, 1996 amendment. We understand that our response will be considered a minor amendment. In reply to your observations, we are providing the following information and support documentation. (The Agency's comments are restated in bold italics with our response(s) immediately following.)

COMMENT

1. *The probability of two or more polymorphic forms of the bulk drug substance requires an analytical method/specification to assure the release of the correct polymorphic drug substance to drug product manufacture. Please define an analytical methodology and specifications/limits for Terazosin Hydrochloride bulk drug substance.*

RESPONSE

In accord with our July 24th discussion with Agency representatives (Dr. A. Mueller and Dr. P. Schwartz), we are instituting a requirement for an identification test based on

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583

Miami • Ft. Lauderdale • Cidra, P.R. • St. Croix, U.S. V.I. • Shreveport • Mason • Syosset

This test will assure the release of the desired polymorphic drug substance for use in the manufacture of the drug product.

In support of this new requirement, the melting ranges of lots PD-0822 (used in the biostudy batch, representing the initial polymorphic form) and PD-1108 (representing our substitute form) were studied. The ranges, which were determined by our identification method, are as follows:

PD-0822	°C
PD-1108	°C

Based on this study, Zenith proposes a specification requiring an onset of NLT °C for the melting endotherm. This requirement will be determined by our identification method. Please refer to Attachment 1 of this amendment for the revised drug substance Specification/ Analytical Report incorporating the additional identification test and our proposed method of analysis.

COMMENT

2. *Drug Master File held by has been found deficient and the holder has been notified.*

RESPONSE

Please refer to Attachment 2 of this amendment for a letter from , stating that has addressed the deficiencies cited in DMF on July 18, 1996

COMMENT

3. *Please submit any and all comparative dissolution data for lots of final drug product made using the newly supplied polymorphic bulk drug substance. If possible, this data should be contrasted to data from batches made using the former polymorphic form of bulk drug substance.*

RESPONSE

We are providing comparative dissolution data for finished product manufactured using the new polymorphic drug substance contrasted to our biostudy batch which was produced with the former polymorphic form. Please refer to Attachment 3, noting a favorable comparison.



COMMENT

The Agency's December 18, 1995, letter from the Division of Bioequivalence recommended the addition of specific dissolution testing. Please submit your most recent specifications of the release of the drug product and for your stability protocol. Please also update these specifications in your test method

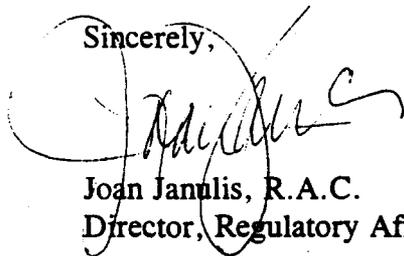
RESPONSE

We have accepted the Agency's recommendation and revised the appropriate documents. Please refer to Attachment 4 for this information.

Additionally, please be advised that Zenith Goldline Pharmaceuticals, Inc. has provided a Field Copy of this amendment to our local district office in accordance with 21 CFR 314.96(b). Attachment 5 of this amendment provides the required Field Copy Certification.

This completes our Minor amendment in response to the Agency's letter of June 24, 1996. We trust that all outstanding deficiencies have been adequately addressed and look forward to the approval of our Abbreviated New Drug Application.

Sincerely,



Joan Janulis, R.A.C.
Director, Regulatory Affairs

enclosures

krij:terazosinmidef2.doc





Zenith Goldline
PHARMACEUTICALS

April 25, 1996

Mr. Douglas L. Sporn
Director
Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED

APR 26 1996

GENERIC DRUGS

N/AM

FPL

AMENDMENT

MINOR AMENDMENT

RE: Terazosin Hydrochloride Tablets
1 mg, 2 mg, 5 mg, and 10 mg
ANDA 74-530

Dear Mr. Sporn:

Reference is made to our pending abbreviated new drug application for Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg, and 10 mg. Reference is also made to the Agency's letter dated March 20, 1996 which described labeling deficiencies, and comments for acknowledgment concerning our Analytical Method

1. We understand that the following response will be considered a MINOR amendment.

Comment:

Labeling Deficiencies

1. *CONTAINER (100s, 500s and 1000s): Satisfactory in FPL.*
2. *INSERT: (minor revisions)*

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

Response:

We have revised our package insert in accord with your recommendations and have included in Attachment 1, twelve (12) copies of the final printed insert for your review.

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583

Miami • Ft. Lauderdale • Cidra, P.R. • St. Croix, U.S. V.I. • Shreveport • Mason • Syosset

Comment:

On completion of the validation of this ANDA for both the Drug Substance and the 5 mg Tablets, the FDA Analyst has these comments and concerns about Analytical Method

1. *There should be a statement in the method indicating that only one injection will be made on each sample and standard vials. (No multiple injections on one vial should be made.)*

2. *The _____ rate for the column should be specified before adjusting the _____ rate from the*

Response:

We acknowledge Comment 1 and have added a note to method indicating that only one injection may be made per sample or standard vial. (This will be submitted in our first annual report.)

Regarding Comment 2, the _____ rate is adjusted in accordance with the instrument manufacturer's directions. (Please note that

- A. The _____ controller is set to the OFF position, and the _____ is adjusted to the desired flow of _____ mL/minute (measured at the _____)

- B. The desired column head pressure is set using _____ controls.

- C. The _____ controller is set to the ON position and the total _____ is adjusted to the desired total _____ rate (measured at the _____)

Based on the training received from our _____ service representative, we feel that this approach to flow rate adjustment is suitable for the method.

ADDITIONAL INFORMATION

We now refer to our 4/16/96 telephone conversation with the Agency (Ms. A. Weikel), during which we discussed providing, with this minor amendment, justification for the substitution of a different crystalline form _____ of the active ingredient, terazosin hydrochloride. We have been notified by our bulk drug substance manufacturer _____ that in the process of scaling down terazosin hydrochloride from a _____ kg batch size to a _____ kg batch size, a different crystalline form was produced. We understand from our supplier that no process or equipment changes have been made during scale down; only the amount of material being processed has been reduced to one third of the original batch size. We have also been assured that the scale down process consistently and reliably produces the new crystalline form.



Office of Generic Drugs
ANDA 74-530
April 25, 1996
Page 3

We intend to substitute (for legal reasons) the new polymorphic form for the form originally submitted. As discussed with FDA on 4/16, we understand that the only requirement for substitution of the new polymorph is comparable solubility between the two forms. Please refer to Attachment 2, which includes our "Technical Report for Dissolution Study of Terazosin Hydrochloride Raw Material Lot #'s PD-0822 and PD-1108" (Report #TRZ-041996). We have also provided a side-by-side comparison of complete test results for Lot PD-0822 (used in the bio-batch) and Lot PD-1108 (material from bulk scaled down batch). These reports clearly justify the substitution of the new form of the bulk drug substance for future manufactured lots of the drug product.

Also, per our 4/16/96 telephone conversation with the Agency, we understand that the inclusion of this additional information regarding the substitute, will not affect the MINOR status of this amendment. We believe that all issues contained in your March 20, 1996 "not approvable" letter have been addressed and look forward to approval of this application.

Sincerely,



Karen Rocco
Associate Director
Regulatory Affairs

trj:\terazon\minorand.doc





Zenith Goldline
P H A R M A C E U T I C A L S

07 August 1995

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

NC

RE: ANDA 74-530
Terazosin Hydrochloride
1 mg, 2 mg, 5 mg and 10 mg Tablets

NEW CORRESPONDENCE

Dear Sir/Madam,

Reference is made to our abbreviated new drug application submitted for the above product on August 1, 1994 and our July 18, 1995 Amendment.

Our July 18, 1995 Amendment included specifications for Lactose Monohydrate NF (pp 48-51) and Corn Starch NF (pp 60-62). Both monographs were updated to USP 23/NF18 and included new specifications for particle size distribution and tapped bulk density, as per your request of January 5, 1995. Through an oversight, we submitted copies of the updated specifications which did not contain the assigned issue dates. Therefore, we are enclosing as New Correspondence, new specification/analysis forms for Lactose Monohydrate NF and Corn Starch NF, identical to those submitted in our July 18, 1995 amendment, however, now reflecting the assigned issue dates.

We apologize for any inconvenience this may have caused.

Sincerely,

ZENITH LABORATORIES
Robert J. Monaghan
Director, Regulatory Affairs

ATTACHMENTS

RECEIVED
AUG 08 1995
GENERIC DRUGS

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583

Miami • Ft. Lauderdale • Cidra, P.R. • St. Croix, U.S. V.I. • Shreveport • Mason • Syosset



Zenith Goldline

PHARMACEUTICALS

*FPL
Contains
(100, 200, 500, 1000)
for your use from 11/2/95*

AMENDMENT

18 July 1995

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 74-530
Terazosin Hydrochloride
1 mg, 2 mg, 5 mg and 10 mg Tablets

MAJOR AMENDMENT

Dear Sir/Madam,

Reference is made to our abbreviated new drug application submitted for the above reference product on August 1, 1994 and our September 12, 1994 Amendment. Reference is also made to your deficiency letter dated January 5, 1995.

At this time we are amending our application with a response to the deficiency comments relating to ANDA 74-530 for Zenith's 1 mg, 2 mg, 5 mg and 10 mg Terazosin Hydrochloride Tablets. The Agency's comments are restated below in italics followed by Zenith's response. We understand that this is considered a major amendment. A copy of this information has been forwarded to our District Office in accordance to 21 CFR 314.94(d)(5) (copy of cover letter and certification statement attached).

A. Chemistry Deficiencies:

- Please add a test for the identification of chloride to the testing protocol of Terazosin HCl drug substance. In addition, please provide the particle size distribution profile for batch PD-0822.*

RECEIVED

RESPONSE:

JUL 20 1995

- As requested, an identification test for chloride has been added to our raw material specification/analysis report for Terazosin HCl. We have also provided chloride test data from the lot of active raw material that was used in the manufacture of the submission batches. Please refer to SECTION VIII for copies of these data and specification revision.

GENERIC DRUGS

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583

Miami • Ft. Lauderdale • Cidra, P.R. • St. Croix, U.S. V.I. • Shreveport • Mason • Syosset

*25 Jul 95
M. Miller*

b.) The particle size distribution profile for batch PD-0822 follows:

Particle Size Distribution for Batch PD-0822

Particle size (µm)	Trial 1	Trial 2	Mean
2-13	16.8	20.1	18.4
14-27	24.9	25.3	25.1
28-53	37.5	34.1	35.8
54-75	14.8	17.1	16.0
76-106	5.4	2.8	4.1
107-150	0.0	0.0	0.0
151-300	0.0	0.0	0.0
Total	99.4	99.4	99.4
DV*	0.0126	0.0123	
Smallest particle	<2 µm	3.3 µm	
Largest particle	106 µm	106 µm	

* DV = value proportional to the amount of sample in the system
Note: each trial is the average of two readings.

(specification: NLT % µm, NMT % µm)

2. Please provide new COAs, from yourself and your supplier, which demonstrate that Lactose meets the new monograph for Lactose Monohydrate NF (USP 23/NF18, p. 2258). In addition, please update the specifications for lactose to the USP monograph, and add the tests and specifications for particle size distribution and tapped density to your testing protocol.

RESPONSE:

- a.) We have provided new certificates of analyses (Zenith and vendor) from a recently received lot of Lactose Monohydrate NF (Zenith code 0651, lot 045058) which demonstrates conformance to USP 23/NF 18 (see SECTION VIII).
- b.) As requested, we have updated our specification for Lactose Monohydrate NF to include tests and specifications for particle size distribution and tapped density. Copies of the test methods are also provided for review (see SECTION VIII). However, we are unable to provide test results on the lot of Lactose Monohydrate NF that was used in the manufacture of the submission batch since retain samples are being used to satisfy forensic sampling requirements. In lieu of these results, we have provided a copy of our technical report which characterizes particle size and tapped density requirements based on data from five lots of vendor material. The test results and report are provided in SECTION VIII.



3. *Please add tests and specifications for particle size profile and tapped density to your testing protocol for corn starch.*

RESPONSE:

As requested, we have updated our specification for Corn Starch NF to include tests and specifications for particle size distribution and tapped density (SECTION VIII). As with our lactose monohydrate, retains have been reserved for forensic testing and we refer to the technical report in SECTION VIII which contains the relevant qualifying data on corn starch.

4. *Please provide comparative IR spectra for crospovidone (sample vs. reference)*

RESPONSE:

A copy of the IR spectra for the lot Crospovidone NF used in the manufacture of the submission batches (Lot PD 0737), with accompanying standard, is provided in SECTION VIII.

5. *Please provide a COA for Colloidal Silicon Dioxide, which demonstrates that the excipient meets the specifications of organic volatile impurities.*

RESPONSE:

We refer to a letter from our supplier of Colloidal Silicon Dioxide NF, dated October 24, 1994 which attests to the absence of OVIs in their raw material and to certificate of analysis which states conformance to USP 23/NF 18. (SECTION VIII).

6. *Please provide reference and sample IR spectra for the colors Titanium Lake Blend (pink) and Pigment Blend Yellow. Please also demonstrate that Pigment Blend Yellow meets the specifications set forth in 21 CFR 73.1200 of the regulations for arsenic, lead and mercury. Please also demonstrate that elemental iron in the 5 mg tablet consumed with the prescribed dosage shall not exceed 5 mg/day.*

RESPONSE:

- a.) Reference and Sample IR spectra for Titanium Lake Blend Pink and Pigment Blend Yellow are provided in SECTION VIII.
- b.) Zenith Laboratories has revised its specification for Pigment Blend Yellow to include USP Tests and specifications for arsenic, lead and mercury. In addition, we have provided test data from the lot of Pigment Blend Yellow used in the manufacture of the submission batch which demonstrate conformance to these specifications (see SECTION VIII). We also refer to the regulatory compliance statements on literature which state conformance to current USP and 21 CFR requirements.



RESPONSE (continued):

c.) In regard to elemental iron, the usual recommended dosage of Terazosin HCl is 1-5 mg administered qd, however, in some cases up to 20 mg administered qd can be prescribed[†]. The yellow lake blend used as a colorant in Zenith's Terazosin contains approximately _____ mg tablet with the elemental iron content making up approximately _____ % w/w. Taking into account a worse case scenario of 20 mg (4 x 5 mg tablets) administered qd, the maximum amount of elemental iron ingested on a daily basis would be approximately _____ mg, well under the 5 mg/day limit.

7. *Please provide data to demonstrate that Magnesium Stearate NF passes the required test for organic volatile impurities.*

RESPONSE:

Although Zenith's specification for magnesium stearate contains a provision to test for OVIs in the raw material, this OVI testing is waived based upon the letter from _____ (supplier for _____ dated June 12, 1995, which confirms the absence of OVIs in their magnesium stearate (see SECTION VIII).

8. *Please describe exactly where in the blend each dosage unit was sampled for blend uniformity. Please justify that the number of samples taken is sufficient to determine the uniformity of the active ingredient in each of the blends that were manufactured for this application. We request that the specification for the mean, whether it be the mean of 10, 20, 30 or some other number of units tested, is between 90.0% and 110%, and the specification for individual units is between 85.0% and 115.0%.*

RESPONSE:

- a.) Please refer to a diagram provided in SECTION XII which specifies the location of the blend uniformity samples.
- b.) As shown in the diagram, seven (7) samples, each sample equivalent to a unit dose size, are taken from each cross-section (top, middle and bottom) of both arms of the blender for a total of 42 samples. The diversity of sampling sites throughout the V-blender, combined with the number of samples taken from each site and the unit dose sample size, assures an adequate representation of the blend. The acceptability of finished product release data (i.e. content uniformity and dissolution) from each of the submission batches clearly demonstrate the adequacy of the sampling plan for blend uniformity.

In addition, this same sampling plan for blend uniformity has been extensively reviewed during various site inspections for other products manufactured at this facility and found to be acceptable.

[†] Physician's Desk Reference, 49th Edition, 1995, page 436, see indications for "Hypertension".



RESPONSE (continued):

Based on the above, we believe our in-process sampling plans are adequate to qualify the blend uniformity.

- c.) The specifications for in-process validation testing has been revised to reflect a mean (n=10) blend uniformity specification of between 90% - 110% and an individual blend uniformity specification of between 85%-115% (see SECTION XII for revised specifications).
9. *Please provide specifications for the in-process blend tests of pour bulk density, tapped bulk density and moisture.*

RESPONSE:

Please refer to SECTION XII.

10. *Please provide the individual, rather than the average, in-process tablet data for hardness, thickness and weight variations for each of the batches that were manufactured for this application. This data may be provided on control charts.*

RESPONSE:

Data is provided in SECTION XI.

11. *Please add a second identification test for Terazosin Tablets. The second test should be able to identify the structure of the active ingredient. We recommend infrared spectrophotometry.*

RESPONSE:

We have adopted an IR method as a second identification test for Zenith's Terazosin Tablets. This method, _____ is provided in SECTION XV along with revised finished product specifications and test data on submission batch retains (ND 190, ND 192, ND 193 and ND 194) for the 1 mg, 2 mg, 5 mg-and 10 mg Tablets, respectively.

12. *The system suitability tests in methods, _____ should include specifications for tailing (t), resolution (R) and column efficiency (theoretical plates) (N). The resolution factor should be determined between the terazosin peak and the peak for _____*

RESPONSE:

The following analytical methods have been revised to include system suitability test specifications for tailing (t), resolution(R) and column efficiency (theoretical plates)(N), as well as a resolution factor determination of not less than 2 between



RESPONSE (continued):

the terazosin peak and the

* The Agency had requested _____ to be revised as indicated above. However, this report does not exist nor was it filed with the ANDA. We believe it was the reviewer's intent to reference _____ (Impurities/degradants for the finished product), and as such, we have revised this method accordingly and provided it for review.

** Although not specifically requested, the system suitability specifications for method _____ (assay for blend analysis) were also revised and are included for review.

Please refer to SECTION XVI for a copy of the above listed analytical reports.

13. *The release specification for _____ should be changed to a specification for any individual impurity or degradant and reduced from NMT _____ % to NMT _____ % each. The specification for total impurities should remain as is.*

RESPONSE:

We have changed our release specification for impurities/degradant to read as follows:

<u>TEST</u>	<u>SPECIFICATION</u>
A.	A. NMT %
B. Other individual impurities/ degradants	B. NMT % each
C. Total impurities/degradants	C. NMT %

Copies of our revised finished product and stability specification sheets for the 1 mg, 2 gm, 5 mg and 10 mg tablets are provided in SECTION XV.

14. *Please explain why the in-process and release data for uniformity of dosage units and dissolution are the same. Please provide new COAs for batches ND-190 (1 mg), ND-192 (2 mg), ND-193 (5 mg), and ND-194 (10 mg), if appropriate.*



RESPONSE

It is our practice to perform testing on our ANDA submission batches beyond what is normally required for finished product release, since this data is considered as the basis for comparison and evaluation of our validation batches. This same data for the finished tablets is reported in both the Finished Product Section (Section XV) and the In-Process Section (Section XII) of our ANDA submission since it can be used to support both finished product release and In-Process/Validation evaluation. Additional and separate testing was not deemed necessary. Please note that the finished product specifications were met despite the larger in-process sample size (i.e. 30 vs. 10 for uniformity and 12 vs. 6 for dissolution), and tighter release specifications (RSD NMT % for 30 in-process units vs. RSD NMT % for 10 release units).

15. *Please include a request for a categorical exclusion under 21 CFR 25.24 (c) (1) of the regulations, or file an appropriate environmental assessment as described under the same set of regulations.*

RESPONSE:

See SECTION XX for a request for a categorical exclusion pursuant to 21 CFR 25.24 (c)(1).

B. Labeling Deficiencies:

We have revised our labels and package insert in accord with your recommendations. Please refer to SECTION V for final printed container labeling and draft copies of our package insert.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. *We acknowledge submission of a process validation protocol. Please note that the final determination of the adequacy of the process validation data is the responsibility of the District Office.*

RESPONSE:

We acknowledge that the final determination of the adequacy of our process validation data is the responsibility of the District Office. Following completion of our validation studies and reports, we will immediately notify our District Office to arrange for a review of the data.

2. *Please provide any additional ° C stability data available.*

RESPONSE:

Twelve (12) month controlled room temperature stability data is provided in SECTION XVII.



3. *Validation of your analytical method package will be delayed until the Division of Bioequivalence finds the dissolution method acceptable. A satisfactory validation is required prior to approval.*

RESPONSE:

We acknowledge that our analytical method package will be delayed until we submit an acceptable dissolution methodology to FDA's Division of Bioequivalence. Their specific concern regarding our dissolution methodology, cited in their February 24, 1995 letter, is as follows:

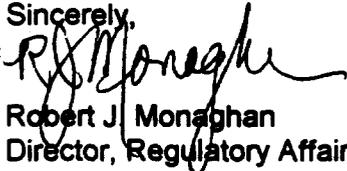
"In-vitro dissolution testing was not conducted in accordance with approved FDA methodology. The methodology utilized is acceptable with the exception of the medium, which should be water instead of 0.1N hydrochloride. Please conduct comparative dissolution testing for all strengths, utilizing the FDA methodology, and submit the results for review."

Zenith Laboratories has responded to FDA's Division of Bioequivalence under separate cover dated July 12, 1995. In response we have revised our dissolution test method to include the use of water as dissolution medium and provided the requested comparative dissolution profiles. Please refer to copies of the FDA's February 24, 1995 deficiency letter and our July 12, 1995 response letter to FDA's Division of Bioequivalence (SECTION VI). Please note that this response letter contains our revised dissolution method and comparative dissolution profiles for Zenith's 1 mg , 2 mg , 5 mg and 10 mg Terazosin HCl Tablets.

We also wish to notify the Agency that the District Office has completed its pre-approval inspection of Terazosin HCl Tablets manufactured at our Northvale, NJ facility and has verbally recommended approval following satisfactory resolution of the dissolution issue.

We believe that all outstanding issues regarding this application have now been addressed and look forward to its approval.

Sincerely,


Robert J. Monaghan
Director, Regulatory Affairs

RK/teraz/response.doc
ATTACHMENTS





Zenith Laboratories, Inc.

YOUR PRESCRIPTION FOR QUALITY

*NAI D/Conroy 9/25/94
checked w/ W. Rumbold
on the patent info
Agree: NAI.*

September 12, 1994

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE

RE: Terazosin Hydrochloride Tablets
1 mg, 2 mg, 5 mg, 10 mg
ANDA 74-530

Dear Sir/Madam:

Reference is made to our pending abbreviated new drug application submitted August 1, 1994 for Terazosin Hydrochloride Tablets. Reference is also made to the Agency's acknowledgement letter dated September 2, 1994, which we received September 9.

In accordance with §505(j)(2)(B)(ii) of the Federal Food, Drug, and Cosmetic Act regarding the Paragraph IV Certification provided in our submission, we have given the required notice to Abbott Laboratories, which is the owner of U.S. patent number 4,251,532 and the holder of approved NDA numbers N19057 and N20223. As per our commitment, we are amending our application with a copy of this notification letter (SECTION III).

Additionally, we are including (in SECTION VIII) a Drug Master File (DMF No. authorization letter from covering the dyes used in the manufacture of our 2 mg and 5 mg tablets, i.e., Titanium Lake Blend Pink and Pigment Blend Yellow, respectively. This document was, regrettably, not included in the original submission.

We appreciate the Agency's consideration of this information.

Sincerely,

ZENITH LABORATORIES, INC.

Nicholas Maselli
Vice President
Regulatory Affairs

RECEIVED
SEP 13 1994
GENERIC DRUGS

kr/terpatfd.ltr

140 Legrand Avenue, Northvale, New Jersey 07647 • (201) 767-1700 (800) 631-1583

Pralex Corporation, Christiansted, St. Croix, U.S. Virgin Islands • Zenith Laboratories Caribe, Inc., Cidra, Puerto Rico

Volume 1 through Volume 6. Volumes 4 through 6 of this Archival Copy include the completed bioavailability study.

The Review Copy is divided into two parts. The first part, contained in red jackets, consists of three (3) volumes, labeled inside as Volume 1 through Volume 3, and includes the Chemistry, Manufacturing, and Controls Technical Sections. The second part, contained in orange jackets, consists of three (3) volumes, labeled inside as Volume 4 through Volume 6, and includes the Bioavailability/Bioequivalence Technical Section.

An *in vivo* bioequivalence study has been conducted on the 5 mg strength through a randomized, single-dose, two-way crossover study in 36 healthy adult male volunteers under fasting conditions. A copy of this study is included with this submission. Although the publication entitled, "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book) lists the 2 mg strength as the reference product, the 5 mg strength was chosen for use in the bioequivalence study. The rationale for this decision is discussed in Section VI of this application. One diskette containing the bio-data is located on the inside front cover of the first volume (Volume 4) of the orange review copy of this application. A bioavailability waiver request for the 1 mg, 2 mg, and 10 mg dosage strengths is also contained in Section VI.

Please note that references to our physical facilities, production equipment, key personnel, and general operating procedures and controls, for the most part, have not been included in this application, in compliance with the OGD Policy and Procedure Guide No. 31-91, dated January 11, 1994. It is our understanding that this information will be reviewed by the local FDA District Office during their inspection process, and will not be requested by the reviewing chemists. In place of the above information, we are providing a brief, general description of our location, operation, and controls in Section IX, as well as appropriate summaries in other sections.

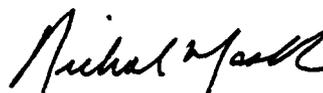
Since Terazosin Hydrochloride is not a USP article, two separately bound copies of the methods validation are being submitted with this application. (See also Section XVI).

Pursuant to 5 USC §552(b)(4) of the Freedom of Information Act and 21 CFR §20.61, regarding privileged and confidential information, we declare that information on Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg, and 10 mg, as to its composition and method of manufacture, constitute trade secrets and confidential commercial information under the law and are, therefore, not disclosable under the Freedom of Information Act.

We respectfully request a review of this application at your earliest convenience.

Sincerely,

ZENITH LABORATORIES, INC.



Nicholas Maselli
Vice President
Regulatory Affairs

Enclosures

35

B:\TERAZ\TERAZCOV.LTR

RECEIVED

AUG 3 1994

GENERIC DRUGS

