CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74657

CORRESPONDENCE

ANDA 74-657

AUG 20 1999

Invamed, Inc.
Attention: Mahendra Patel, Ph.D.
2400 Rt. 130 North
Dayton, NJ 08810

Dear Sir:

This is in reference to your abbreviated new drug application dated April 8, 1995, 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 the Tentative Approval letter issued by this Office on March 7, 1997, and to your amendments dated September 25, and October 1, 1997; September 30, 1998; and July 15, and July 23, 1999.

We have completed the review of this abbreviated application as amended, and have concluded that based upon the information you have presented to date, the drug product is safe and effective for use as recommended in the submitted labeling. Therefore, the application remains 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 (CGMPs) of the facilities used in the manufacture and testing of the drug product), and is subject to change on the basis of new information that may come to our attention.

The reference listed drug product referenced in your application, Hytrin Tablets of Abbott Laboratories Pharmaceutical Products Division, is subject to periods of patent protection which expire on April 29, 2013 (U.S. Patents No. 5,504,207 [the '207 patient] 5,294,615 [the '615 patent], and 5,412,095 [the '095 patent]), June 29, 2010 (U.S. Patent No. 5,212,176 [the '176 patent]) and February 17, 2000 (U.S. Patent No. 4,251,532 [the '532 patent]). With the exception of the '207 patent, all regulatory issues pertaining to these patents were resolved in Invamed's favor upon issuance of the agency's tentative approval letter. Subsequently, Invamed Inc. made a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use or sale of this drug product will not infringe the '207 patent, or that the '207 patent is invalid or unenforceable. Section 505(j)(5)(B)(iii) of the Act provides

that approval of an abbreviated application shall be made effective immediately unless an action for patent infringement is brought before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received by the owner of the new drug application (NDA) for the reference listed drug product (Hytrin Tablets) and the patent holder. You have notified the agency that Invamed Inc. (Invamed) has complied with the requirements of Section 505(j)(2)(B) of the Act and that Abbott Laboratories initiated a patent infringement suit against Invamed in the United States District Court for the Northern District of Illinois - Eastern Division [Abbott Laboratories vs. Invamed, Inc., Civil Action No. 97C7587 (N.D. III)]. You have also notified the agency that on August 28, 1998, the court entered summary judgement for Invamed in that lawsuit.

However, we are unable to grant final approval for your application at this time. The district courts in both Inwood and Mova held that 180 days of marketing exclusivity should be granted to the first ANDA applicant who files a Paragraph IV Certification, regardless of whether that applicant is subsequently sued for patent infringement. As a result, the agency will not enforce the "successful defense" provision of Section 314.107(c)(1) and the related provision in 314.107(c)(4). Please be aware that an abbreviated application for Terazosin Tablets containing a Paragraph IV Certification was previously accepted for filing by this Office prior to the filing of your application. Accordingly, your application will be eligible for final approval beginning on the date that is one hundred and eighty (180) days after (1) the date the Secretary receives notice of the first commercial marketing of the drug under the previous application; or (2) the date of a decision of a court holding the remaining patents which have not the subject of a court decision to be invalid or not infringed, whichever event occurs first (Section 505(j)(5)(B)(iv). At this time, the agency does not believe that the provisions of either (1) or (2) have been met. We refer you to the Agency's recently issued guidance document entitled "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, please submit an amendment at least 60-days but not more than 90-days prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the drug product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing and controls data as appropriate. Alternatively, this amendment should be submitted stating that no changes have been made to the terms of the application since the date of this second tentative approval. This amendment should be designated

clearly in your cover letter as a MINOR amendment. In addition to, or instead of this amendment, the Agency may request at any time prior to the date of final approval of this application that you submit an amendment containing the information described above. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

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

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.

Prior to submitting the amendment(s), please contact Ruby Yu, Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

/S/

Douglas L. Sporn 8/18/99
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-657

Invamed Inc.
Attention: Dr. Mehendra Patel
2400 Rt. 130 North
Dayton, NJ 08810

Dear Sir:

Reference is made to your abbreviated new drug application dated April 8, 1995, 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 (base). The application contains certifications under section 505(j)(2)(A)(vii)(III) and (IV) of the Act.

Reference is also made to your amendments dated July 15, August 12, August 26, September 6, September 25, October 12, November 22, December 14 and December 23, 1996, and March 6, 1997.

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, which includes information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug products. Therefore, this determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product referenced in your application is subject to a period of patent protection and therefore, final approval cannot be granted pursuant to 21 U.S.C. 355 (j)(4)(B)(ii), until the period has expired, i.e., April 29, 2013 (patent 5,504,207).

Please provide the Agency, at least 60, but not more than 90 days prior to April 29, 2013, an amendment to this application. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved and should include updated information such as labeling, chemistry, manufacturing and controls data as appropriate. This submission should be designated as a MINOR AMENDMENT in your cover letter.

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

Failure to submit such an amendment requested by the Agency will prompt a review of the application which may result in rescission of this tentative approval letter.

Any significant change in the conditions outlined in this abbreviated application requires Agency approval before the change may be made effective.

Prior to the issuance of a final approval letter by the Agency your product is not to be deemed approved for marketing under 21 U.S.C. 355 and not to be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to April 29, 2013, you should amend your application accordingly.

At the time you submit any amendments, please contact Sheila M. O'Keefe, Project Manager, at (301) 594-0370, for further instructions.

The introduction or delivery for introduction into interstate commerce of the drug before the effective approval date is prohibited under 21 U.S.C. 311(d).

Sincerely yours,

/S/ 3/7/57

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

ANDA 74-657

Food and Drug Administration
Attention: Mr. Matthew Lewis, District Director, MAY 15 1996
NWJ-DO, HFR-MA300
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Dear Sir:

Invamed Inc., has submitted their regulatory methods for Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg. Therefore, these proposed regulatory analytical methods should be validated by an FDA laboratory since this subject drug substance and product do not have USP monographs.

As instructed under the PRE-APPROVAL INSPECTION/INVESTIGATIONS program (7346.832) you are requested to collect samples of the subject drug substance and product, including the reference standards, from the applicant's laboratory at the following address:

Invamed, Inc.
2400 Rt. 130 North
Dayton, NJ 08810

We have included a copy of the methods validation package for this drug substance and product. Please have the investigator collect the samples and standards from the above address. We recommend that the validation be conducted on the lowest strength.

Upon completion of the district's portion of the methods validation, please send worksheets, all attachments, conclusions, and recommendations directly to the review chemist, Mr. Stephen Sherken (OGD, HFD-625, Room 237), within five days of completion. If you have any additional questions, please call him at (301) 594-0370.

Sincerely yours,

/S/ 5/15/96

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

ANDA 74-657

Invamed Inc.
Attention: Dr. Mehendra Patel
2400 Rt. 130 North
Dayton, NJ 08810

Dear Sir:

This is in reference to your abbreviated new drug application dated April 8, 1995 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Terazosin Tablets, 1, 2, 5 and 10 mg.

Reference is also made to your amendments dated October 24, and December 21, 1995 and April 12, 1996.

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

A. Chemistry Deficiencies:

DMF is still deficient. The DMF holder has been notified. Please confirm their response to our communication.

B. Labeling Deficiencies:

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

Satisfactory in final print.

2. INSERT

GENERAL COMMENT

Due to GATT patent extension from September 5, 1995, to January 21, 1997, your insert labeling should be revised to include all information pertaining to the exclusivity for "Treatment of symptomatic benign prostatic hyperplasia", which expires September 29, 1996. In addition, you should amend your application as appropriate.

Please revise your labels and labeling, as instructed above, and submit final printed insert labeling. To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

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

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

1. Please submit additional stability data accrued to date, if available.

2. The analytical methods that are to be validated by the FDA will be sent to the local FDA District from this Office. No further action on your part is required at this time. A satisfactory validation is necessary prior to approval of the ANDA.

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/ - 5/14/96

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

cc: ANDA 74-657
Dup File
Division File
Field Copy
HFD-600/Reading File

Endorsements:

5/14/96 - 5/14/96

HFD-625/SSherken/5/2/96
HFD-625/MSmela/5/3/96
HFD-617/SO'Keefe/5/6/96 5/14/96 5/14/96
HFD-613/CZimmermann/5/8/96
HFD-610/JPhillips/5/9/96 e 5/13/96

NOT APPROVABLE MINOR AMENDMENT

ANDA 74-657

Invamed Inc.
Attention: Dr. Mahendra Patel
2400 Rt. 130 North
Dayton, NJ 08810

NOV 22 1995

Dear Sir:

This is in reference to your abbreviated new drug application dated April 8, 1995, 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 (base).

Reference is also made to your amendments dated April 29, May 3, and July 11, 1995.

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

A. Chemistry Deficiencies:

1. The specifications used with say that an spectrum of the test preparation is to be in concordance to that of a USP reference standard. Presently, the USP doesn't have a USP reference standard. Please clarify.

2. Please provide copies of of the sample preparation and the standard preparation used to identify Terazosin Hydrochloride with Test B.

3. In regard to the in-process control of the hardness measurements, please modify the frequency of testing for hardness from 3 tablets every hour to 5 tablets every half hour. Additionally, the upper limit of your hardness ranges should be lowered consistent with the data from the exhibit batches.

4. We request that you test all batches for blend uniformity. We believe that at least 10 samples should be extracted from different points of the blender to determine the uniformity of the active ingredient. Each sample should be about one equivalent tablet weight. Samples should be taken from the blended material at different levels in the blender and assayed for Terazosin (base). Statistical evaluations should be made to determine blend uniformity. Please add an instruction and specification to the master batch records.

5. Please add a specification for the percent of fine material that passes through the mesh screen for the in-process test of particle size distribution.

6. Please provide letters of authorization to review DMFs from and respectively.

7. Please provide data to show that the heat sealable polyethylene film from 3M's liner, passes the physico-chemical tests in Section <661> of the USP.

8. Please provide complete information and proof of the physical and chemical characteristics of your Terazosin Hydrcchloride Reference Standard. Please include such information that will prove the structural formula of the reference standard, physical and chemical characteristics of the reference standard, and the purity profile of the reference standard. Analytical techniques such as should be employed as needed.

9. Please provide a Stability Protocol for post-approval batches of each strength of tablet placed on stability in your smallest and largest container/closure systems including tests and specifications as shown on pages 3397 to 3408 of the application.

10. The release and stability data indicate that the specifications for individual and total impurities and degradants should be lowered considerably. We suggest that the specification for individual impurities and degradants should be changed from NMT % to NMT %, and the specification for total impurities and degradants from NMT % to NMT %.

11. DMF is deficient. The DMF holder has been notified.

B. Labeling Deficiencies:

CONTAINER (100s, 500s, and 1000s): The strength of this product is expressed in terms of terazosin, and we suggest clarifying it as follows -

1. Include an asterisk after the expression of strength on the main panel.

2. Revise the "Each tablet contains" statement as follows -

*Each tablet contains terazosin hydrochloride

2. Revise the "Each tablet contains" statement as follows -

*Each tablet contains terazosin hydrochloride equivalent to __ mg of terazosin.

INSERT:

1. GENERAL COMMENTS

   a. Use "terazosin" rather than "terazosin hydrochloride" or "terazosin hydrochloride tablets" throughout the text of the insert except in the following sections -

      DESCRIPTION
      INDICATIONS AND USAGE
      HOW SUPPLIED

   b. When expressing a range of values, we prefer the use of "to" rather than a hyphen.

   c. When expressing a number of units, please assure that the number and the units appear on the same line.

2. DESCRIPTION

   a. Paragraph 2 (second sentence) -

      ...in four strengths...

   b. Revise the molecular weight to read -

      423.89
      [NOTE: This is the molecular weight of the anhydrous form]

3. CLINICAL PHARMACOLOGY

   a. Delete the entire text of the first subsection titled
      "A. Benign Prostatic Hyperplasia (BPH)".

   b. Delete the second subsection heading, "B. Hypertension".

      [NOTE: Retain the text.]

4. INDICATIONS AND USAGE

a. First sentence -

Terazosin hydochloride tablets are indicated...

b. Second sentence -

They can be used...

5. WARNINGS

Delete the fourth paragraph, ("In three placebo...").

6. PRECAUTIONS

a. General

1) Delete the entire subsection titled "Prostatic Cancer".

2) Orthostatic Hypotension

Delete the second sentence, ("In BPH...").

b. Information for Patients

Delete "(see Patient Package Insert)" in the subsection heading.

c. Drug Interactions -

methyclothiazide [spelling]

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/m^2/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/m^2). Female rats were unaffected. Terazosin was not oncogenic...at a maximum tolerated dose of 32 mg/kg/day (110 mg/m^2; 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/m^2; 20 times the maximum recommended human dose), and five of 19 male rats given 120 mg/kg (960 mg/m^2; 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. Pediatric Use

...in pediatric patients have...

7. ADVERSE REACTIONS

   a. Delete the entire text of the first subsection titled "Benign Prostatic Hyperplasia".

   b. Delete the subsection heading, "Hypertension".

      [Note: Retain the text].

   c. Revise Table 3 to read Table 1, and Table 4 to read Table 2, along with the references to these tables in the text. Also, delete "HYPERTENSION" from the table headings.

8. DOSAGE AND ADMINISTRATION

   a. Delete the entire subsection titled "Benign Prostatic Hyperplasia".

   b. Relocate the subsection "Use with Other Drugs" to appear at the end of this section.

9. HOW SUPPLIED

   ...terazosin hydrochloride tablets, equivalent to __ mg terazosin, is engraved...

10. Delete the REFERENCES section.

Please revise your container labels and package insert labeling, then 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. Please submit all stability data accrued to date, if additional data are available.

2. A satisfactory compliance evaluation for firms referenced in the application is required prior to approval.

3. Methods Validation by the FDA will be delayed until the Division of Bioequivalence endorses your dissolution method and specifications. 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/ 11/17/95

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

cc: ANDA 74-657
DUP File
Division File
Field Copy
HFD-600/Reading File

11/17/95

11/17/95

Endorsements:
HFD-625/SSherken/11/1/95
HFD-625/MSmela/11/3/95
HFD-617/CSO/O'Keefe/11/9/95
HFD-613/JGrace/11/13/95 11/16/95 11-16-95
HFD-613/JPhillips/11/15/95 J Phillips 11/17/95

NOT APPROVABLE MAJOR AMENDMENT

ANDA 74-657

Invamed Inc.
Attention: Mahendra Patel, Ph.D.
2400 Route 130 North
Dayton NJ 08810

FEB 2 0 1996

Dear Sir:

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

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 you stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of water at 37°C using apparatus 2 (paddle) at 50 rpm. The test products should meet the following specifications:

   > Not less than % of the labeled amount of terazosin hydrochloride 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

ANDA 74-657

Invamed, Inc.
Attention: Mahendra R. Patel, Ph.D.
2400 Route 130 North
Dayton, NJ 08810

MAY 19 1995

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated April 24, 1995, and your amendment dated April 29, 1995.

NAME OF DRUG: Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg, and 10 mg (base)

DATE OF APPLICATION: April 8, 1995

DATE OF RECEIPT: April 10, 1995

DATE ACCEPTABLE FOR FILING: May 1, 1995

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

David Konigstein
Consumer Safety Officer
(301) 594-0370

Sincerely yours,

/S/ 5/19/95

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-657

Invamed, Inc.
Attention: Mahendra Patel, Ph.D.
2400 Route 130 North
Dayton, NJ 08810

APR 24 1995

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated April 8, 1995, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg, and 10 mg (base).

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> You have failed to properly address the patents on the reference listed drug. Please revise your patent certification to reflect the information in Approved Drug Products with Therapeutic Equivalence Evaluations, 15th Edition. The patents #5294615, expiring March 15, 2011, and #5212176, expiring May 18,2010, are specific to NDA 20-347, terazosin hydrochloride capsules. In addition, you state that you do not infringe patent #4251532, expiring February 17, 2000. A Paragraph IV certification "shall be accompanied by a statement that the applicant will comply with the requirements under Section 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with the requirements under Section 314.95(c) with respect to the content of the notice" [21 CFR 314.94(a)(12)(i)(A)(4)]. Please provide a revised patent certification.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/ for /

4-21-95

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-657
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Acting Chief /S/ 4/18/95 date
HFD-615/WRussell, CSO 4/17/95 date
HFD-610/JPhillips, Chief, LRB 4/20/95 date
HFD-625/MSmela, Sup. Chem. 4/12/95 date

ANDA Refuse to File!

invamed inc.
732-274-2400 Fax: 732-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

March 28, 2000

Mr. Peter Rickman
Deputy Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

NC

Re: **ANDA # 74-657**
TERAZOSIN HYDROCHLORIDE TABLETS
(1 mg, 2 mg, 5 mg and 10 mg strengths)
Response to telephone enquiry

Dear Mr. Rickman:

As per a phone conversation of March 24, 2000 with Dr. Dave, I have herewith provided following statement with respect to US Patent 5,212,176 Exp. May 18, 2010:

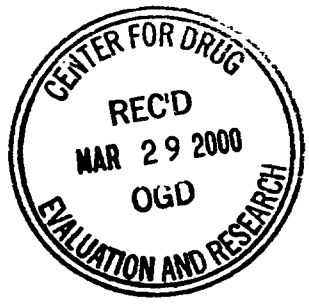
The firm is hereby withdrawing a Patent Certification III submitted in reference to US Patent 5,212,176 from the above referenced ANDA. Please note that this withdrawal is effective due to ***late filing of US Patent 5,212,176.*** Due to this reason no Patent Certification is required for the said patent.

I trust this meets with your approval.

Sincerely,

M. Patel

Mahendra Patel, Ph.D.
Chief Scientific Officer



invamed inc.
732-274-2400 Fax: 732-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

March 25, 2000

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

Re: TERAZOSIN HYDROCHLORIDE TABLETS, 1 mg, 2 mg, 5 mg and 10 mg
ANDA # 74-657
MINOR AMENDMENT TO TENTATIVELY APPROVED ANDA

Dear Sirs

In reference to the telephonic conversation today with Ms. McNeil, we acknowledge that Geneva Pharmaceuticals Inc. has withdrawn their 180-day exclusivity on their Terazosin Hydrochloride tablets ANDA. Therefore, the above referenced ANDA is now eligible for a ***full approval***.

We hereby certify that there are no changes being implemented in the labeling, chemistry, manufacturing and control sections of the referenced ANDA which are not or addressed in the major, minor and/or telephonic amendments submitted to the Office of Generic Drugs, Food and Drug Administration during the review and approval process.

I trust that the information provided herein meets with your approval. As the review clock has already consumed part of the 180-Day cycle, we request that this ANDA should not be subjected to additional review clock.

Sincerely

Mahendra Patel, Ph.D.
Vice-President

invamed inc.
732-274-2400 Fax: 732-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

July 23, 1999

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

NDA ORIG AMENDMENT
N/A

Re: TERAZOSIN HYDROCHLORIDE TABLETS, 1 mg, 2 mg, 5 mg and 10 mg
ANDA # 74-657
TELEPHONE AMENDMENT TO TENTATIVELY APPROVED ANDA

Dear Sirs

With reference to the telephonic conversation today with Ms. Ruby Yu, we hereby certify that there are no changes being implemented in the labeling, chemistry, manufacturing and control sections of the referenced ANDA which are not or addressed in the major and/or minor amendments submitted to the Office of Generic Drugs, Food and Drug Administration during the review and approval process.

I trust that the information provided herein meets with your approval.

Sincerely

M. Patel

Mahendra Patel, Ph.D.
Vice-President

invamed inc.
732-274-2400 Fax: 732-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

July 23, 1999

TELEPHONE AMENDMENT

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

Re: Terazosin Tablets, 1 mg, 2 mg, 5 mg and 10 mg
ANDA 74-657

Dear Sirs

With reference to the telephonic conversation today with Ms. Ruby Yu, we are herewith enclosing details of outside firms including contract testing laboratories and manufacturer/ supplier of Terazosin Hydrochloride towards the tentatively approved ANDA.

Sincerely,

M n Paty.

Mahendra Patel, Ph.D.
Vice President

invamed inc.
732-274-2400 Fax: 732-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

July 15, 1999

Mr. Peter Rickman
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

MINOR AMENDMENT

Re: **ANDA # 74-657**
TERAZOSIN HYDROCHLORIDE TABLETS
(1 mg, 2 mg, 5 mg and 10 mg strengths)

Dear Mr. Rickman:

Reference is made here to a letter received from the Agency dated March 7, 1997. This letter provided a tentative approval to firm's above referenced ANDA.

The reason for granting "Tentative Approval" was subject to Abbott's US Patent 5,504,207 which expires on April 29, 2013.

Please note that in a recent judgement declared in the United States Court of Appeals for the Federal Circuit, Northern District of Illinois, Judge Joan B. Gottschall announced the final ruling stating that Abbott's US Patent 5,504,207 is invalid. The court ruling invalidates Claim 4 of the US Patent 5,504,207. This claim was for the anhydrous form (polymorph) of TERAZOSIN HYDROCHLORIDE which is part of Invamed's tentatively approved ANDA.

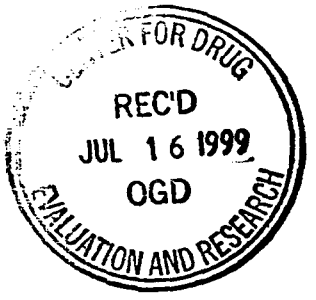
A copy of court ruling is provided herewith for ease of review.

As the anhydrous polymorphic form of Invamed's TERAZOSIN HYDROCHLORIDE is no longer infringing the US Patent 5,504,207, the firm is requesting to grant a "Final Approval" for this ANDA. The firm is also requesting to provide relevant information if this ANDA is subjected to any 180-day exclusivity restrictions. If so, please provide the date from which such an exclusivity period expires.

Sincerely

M. A. Patel.

Mahendra Patel, Ph.D.
Vice President



invamed inc.
732-274-2400 Fax: 732-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

October 20, 1998

NAI
11/3/98
NEW CORRESP
NC

Mr. Gordon Johnston
Deputy Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, Maryland 20855

Re: ANDA 74-657
Terazosin Tablets, 1, 2, 5 and 10 mg

Dear Mr. Johnston:

This is in reference to your telephone conversation of October 19, 1998, regarding Invamed's submission dated September 30, 1998. This submission provided New Information about legal status on the patent matter.

This submission was delivered by overnight Federal Express service (Airway Bill No.802816472690). The package was received at the OGD on October 5, 1998, by M.Firnbacher. Relevant documentation to this effect is attached for your follow up.

A desk copy of the same submission was also sent to Mr. Peter Rickman by overnight Federal Express service (Airway Bill No.802816472705). The package was received at the OGD on October 5, 1998, by M.Firnbacher. Relevant documentation to this effect is attached for your follow up.

I am herewith providing the entire copy of this submission for your review and follow up. Please call me if you need any additional information.

I thank you for your cooperation in this matter.

RECEIVED
OCT 21 1998
GENERIC DRUGS

Sincerely,

Mahendra Patel, Ph.D.
Vice President

10/20/1998

invamed inc.
732-274-2400 Fax: 732-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

September 30, 1998

PATENT AMENDMENT

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

Re: ANDA 74-657, New Information
Terazosin Tablets, 1, 2, 5 and 10 mg

Dear Sirs:

We are writing with respect to our tentatively approved ANDA 74-657 for TERAZOSIN TABLETS, 1, 2, 5 and 10 mg. In sum, Invamed believes that the statutory 30-month delay on ANDA final approval is no longer legally relevant, as the district court entered judgment on August 28, 1998 for Invamed in a patent infringement lawsuit brought by Abbott Laboratories involving U.S. Patent No.5,504,207 ('207 patent). Alternatively, the 30-month bar has already expired, as it started running on May 1, 1995, the date on which Invamed's first notification of non-infringement was received by Abbott. If final approval of Invamed's ANDA must be delayed because another ANDA applicant is entitled to 180-day exclusivity, FDA should recognize and publicly announce that the exclusivity period began running on August 28, 1998, the date of the district court decision, and will expire 180 days later on February 24, 1999.

I. "COURT" MEANS DISTRICT COURT

By letter dated September 25, 1997, Invamed submitted a Paragraph IV certification with respect to the '207 patent, contending, in part, that Claim 4 of the '207 patent is invalid because terazosin hydrochloride was on sale more than one year before the filing date of the patent application. On September 25, 1997, Invamed also notified Abbott of the filing of the Paragraph IV certification. Abbott received that notice on September 29, 1997. (Documentation of these events is already in our ANDA file.)

Abbott brought a patent infringement lawsuit against Invamed within the 45-day window pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), thereby triggering the 30-month automatic delay on final approval of Invamed's ANDA. On August 28, 1998, the United State

District Court for the Northern District of Illinois entered summary judgment for Invamed in that patent infringement lawsuit, Abbott Laboratories v. Invamed, Inc. No. 97C-7587 (N.D. III).[1] Copies of the district court's Memorandum Opinion and Order and Judgment in a Civil Case are enclosed. The district court held that Claim 4 of the '207 patent is invalid because Form IV terazosin hydrochloride (the subject of the '207 patent) was on sale, within the meaning of 35 U.S.C. § 102(b), more than one year before Abbott filed its patent application.

The relevant statutory provision, 21 U.S.C. § 355(j)(5)(B)(iii), reads, in relevant part, as follows:

> If such [a patent infringement] action is brought before the expiration of [the 45 day period after receipt of the notification of non-infringement], the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice [of non-infringement]...except that --
>
> (I) if before the expiration of such period the court decides that such patent is invalid or not infringed, the approval may be effective on the date of the court decision.

(Emphasis added.)

In a September 15, 1997 decision, the United States District Court for the District of Columbia in TorPharm Inc. v. Shalala, 1997 U.S. Dist. LEXIS 21983 (D.D.C. 1997) (copy enclosed), held that the reference to "the court" in the quoted provision is to "the court that decides that the patent is invalid or not infringed," namely, the district court. Although an appeal of this decision was withdrawn by agreement of the parties, and the September 15, 1997 Opinion and Order were vacated on remand, Invamed believes that the decision represents the proper interpretation of § 355(j)(5)(B)(iii). Properly interpreted, the 30-month automatic bar to final ANDA approval is no longer of any legal relevance, as the U.S. District Court for the Norther District of Illinois entered judgment on August 28, 1998 in Abbott Laboratories v. Invamed, Inc., holding that the '207 patent is invalid.

---

[1] Abbott's patent infringement lawsuits against Geneva Pharmaceuticals, Inc. (Abbott Laboratories v. Geneva Pharmaceuticals, Inc., No. 96C-3331 (N.D. III)) and Novopharm, Limited (Abbott Laboratories v. Novopharm Limited, No. 96C-5868 (N.D. III)) were consolidated with its suit against Invamed. The district court's decision applies to all three cases.

Except for possible 180-day exclusivity (discussed in Section III below), there is no impediment to final approval of Invamed's ANDA.

II. DOCTRINE OF "RELATION BACK"

Second, and in the alternative, the 30-month bar to approval of Invamed's ANDA has already expired because the full 30-month period has run. Specifically, Invamed submitted a Paragraph IV certification for this ANDA on April 29, 1995, and so notified Abbott on that date. Abbott received that notification on May 1, 1995. (Again, documentation of these events is already part of our ANDA file). Thereafter, Abbott brought a patent infringement lawsuit against Invamed within the 45-day statutory window, Abbott Laboratories v. Invamed, Inc., No. 95C-03484 (N.D. III), triggering the 30-month delay of ANDA approval.

For purposes of the 30-month bar, Invamed's September 1997 notice to Abbott about the filing of a Paragraph IV certification on the '207 patent relates back to the date of its initial notice to Abbott of non-infringement in 1995. The 30-month period, which started running on May 1, 1995 (the date on which Abbott received Invamed's notification of the Paragraph IV certification), expired on November 1, 1997.

Except for possible 180-day exclusivity (discussed in Section III below), there is no impediment to final approval of Invamed's ANDA.

III. THE 180-DAY EXCLUSIVITY PERIOD HAS ALREADY BEGUN TO RUN

We assume only for purposes of this request to issue a final approval for ANDA 74-655 that another firm may be eligible for 180-day exclusivity for generic terazosin tablets, 1, 2, 5 and 10 mg, because that firm was the first Paragraph IV ANDA applicant for generic terazosin tablets and it was sued for patent infringement, as required by 21 U.S.C. § 355(j)(5)(B)(iv) and the decision of the U.S. Court of Appeals for the District of Columbia Circuit in Mova Pharmaceutical Corp. v. Shalala, 140 F.3d 1060 (D.C. Cir. 1998).[2] If that is the case, and FDA cannot grant Invamed final ANDA approval, effective immediately, FDA must recognize -

---

[2] If the first Paragraph IV ANDA applicant for generic terazosin tablets was not sued for patent infringement, it is Invamed's position that no firm is entitled to 180-day exclusivity. Invamed's position on this issue is currently before the U.S. Court of Appeals for the District of Columbia Circuit in Purepac Pharmaceutical Co. v. Friedman, Nos. 98-5334, 98-5335, and 98-5337, scheduled for oral argument on November 3, 1998. That position is well-known to FDA. In the interest of brevity, it will not be repeated here.

- and publicly announce -- that the 180-day exclusivity period began running on August 28, 1998. That conclusion follows directly from § 355(j)(5)(B)(iv)(II), which provides that the 180-day period starts with "the date of a decision of a court in an action described in clause (iii) holding the patent which is the subject of the certification to be invalid or not infringed" (emphasis added). As stated above, the well-reasoned holding in TorPharm Inc. v. Shalala defines the relevant date as the date of the district court decision finding the patent invalid or not infringed. Thus, if another ANDA applicant for terazosin tablets is entitled to 180-day exclusivity, Invamed's ANDA is entitled to receive final approval no later than February 24, 1999, 180 days after the date of the district court decision in Abbott Laboratories v. Invamed.

* * *

Invamed requests an agency response to this letter by October 30, 1998. If Invamed does not receive a response by that time, we will view the agency's failure to respond as a denial and will pursue our available legal options. We appreciate the agency's attention to this important matter.

Respectfully submitted,

M. Patel

Mahendra Patel, Ph.D.
Vice President

ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500

NEW CORRESP

September 28, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
7500 Standish Place, Rm. 150
Rockville, MD 20855

RE: **ANDA Nos. 74-315, 74-446, 74-657**
Abbott Labs. v. Geneva Pharmaceuticals, Inc., 96 C 3331
Abbott Labs. v. Novopharm Led., 96 C 5868
Abbott Labs. v. Invamed, Inc., 97 C 7587

Dear Sir/Madam:

Abbott Laboratories timely sued the sponsors of the above-referenced ANDAs based on their "Paragraph IV" certifications under 21 U.S.C. § 355(j)(2)A)(vii)(IV). The ANDAs seek approval to market 1 mg, 2 mg, 5 mg and 10 mg terazosin hydrochloride tablet generic versions of Abbott's Hytrin®.

This letter is to advise FDA that (I) the district court hearing the above-referenced cases has held that claim 4 of the '207 patent is invalid, and (ii) Abbott has timely appealed the district court's decision. Accordingly, the prohibitions on FDA approval of these ANDAs remain in effect. 21 U.S.C. § 355(j)(5)(B)(iv); 21 CFR § 314.107(b),(c),(e).

Should you have any questions concerning this submission, please do not hesitate to contact me directly.

Sincerely,
ABBOTT LABORATORIES

Marilou Reed

Marilou Reed
Associate Director, Regulatory Affairs
(847) 937-6844, fax (847) 937-8002

cc: Division of Cardio-Renal Drug Products, HFD-110
Central Document Room, 12229 Wilkins Avenue
Division of Data Management and Services, HFD-090

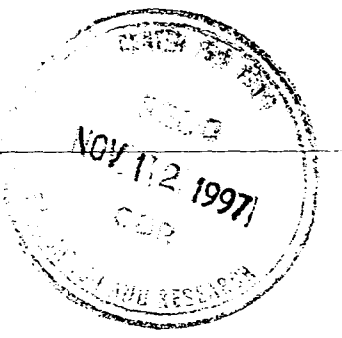
RECEIVED
SEP 30 1998
GENERIC DRUGS

Madlw
10-1

ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500



October 31, 1997

NEW CORRESP

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
7500 Standish Place, Rm. 150
Rockville, Maryland 20855

RE: Abbott Laboratories v. Invamed, Inc.
ANDA 74-657

Gentlemen:

ANDA 74-657 filed by Invamed, Inc. ("Invamed") contains a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) asserting that the manufacture, use and sale of its terazosin hydrochloride tablets 1 mg, 2 mg, 5 mg, 10 mg generic versions of Abbott's Hytrin® does not infringe a United States patent owned by Abbott Laboratories ("Abbott") on the grounds that the patent is invalid and unenforceable. Specifically, the certification is to U.S. Patent No. 5,504,207. Notice of this certification was received by Abbott on September 29, 1997.

This letter is to advise FDA that on October 28, 1997, Abbott filed a lawsuit against Invamed in federal district court in Chicago, Illinois, (case number 97 C 7587) alleging infringement of the above-referenced patent. A copy of the lawsuit is enclosed.

Because Abbott has filed its action within 45 days of receipt of notice of the certifications, pursuant to the Federal Food, Drug and Cosmetic Act, §505(j)(4)(B)(iii), **the agency cannot approve ANDA 74-657 until "the expiration of the thirty-month period beginning on the date of the receipt of the notice...**or such shorter or longer period as the court may order..."

Should you have any questions concerning this matter, please feel free to contact me directly.

Sincerely,
ABBOTT LABORATORIES

Marilou Reed

Marilou Reed
Associate Director, Regulatory Affairs
D-491, AP6B/1
(847) 937-6844

cc: Division of Cardio-Renal Drug Products, HFD-110
Central Document Room, 12229 Wilkins Ave., Rockville, MD
Drug Information Services Branch, HFD-84

RECEIVED
NOV 13 1997
GENERIC DRUGS

invamed inc.

NEW CORRESP
N/NC

732-274-2400 Fax: 732-274-8989

2400 Rt. 130 North, Dayton, New Jersey 08810

October 1, 1997

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **ANDA# 74-657**
TERAZOSIN TABLETS, 1 mg, 2 mg, 5 mg and 10 mg
Correspondence to the application

Dear Sirs

I have herewith enclosed (in duplicate) a copy of patent non-infringement notification served to Abbott Laboratories as required under 21 CFR 314.95 (a) for a tentatively approved Abbreviated New Drug Application (ANDA # 74-657) for ***TERAZOSIN TABLETS, 1 mg, 2 mg, 5 mg and 10 mg.***

Please note that this notification was received by Abbott Laboratories on September 29, 1997. A copy of relevant documentation for the receipt of this document is provided for ease of review.

Sincerely

M. Patel

Mahendra Patel, Ph.D.
Vice President

invamed inc.
732-274-2400 Fax: 732-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

September 25, 1997

NEW CORRESP
NC

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

Re: **Terazosin Tablets, 1, 2, 5 and 10 mg**
ANDA # 74-657
Correspondence to the application

Dear Sirs

I have herewith enclosed a "***Correspondence to the application***" document to our tentatively approved application for **TERAZOSIN TABLETS, 1, 2, 5 and 10 mg (ANDA # 74-657)**.

The firm is providing a new Paragraph IV Patent Certification towards Abbott's patent 5,504,207 through this submission.

Sincerely

Mahendra Patel, Ph.D.
Vice President

RECEIVED
SEP 26 1997
GENERIC DRUGS

9-26-97

invamed inc.
908-274-2400 Fax: 908-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

December 23, 1996

Mr. Peter Rickman
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

Re: **ANDA # 74-657**
TERAZOSIN HYDROCHLORIDE TABLETS
(1 mg, 2 mg, 5 mg and 10 mg strengths)
Additional Information on Case 95C7185

Dear Mr. Rickman

Enclosed herewith please find complete documentation for Case No. 95C 7185 between Abbott Laboratories and Invamed Inc.

Invamed Inc. served Paragraph IV Certification Notice to Abbott Laboratories on October 31, 1995 covering Abbott's Patent(s) 5,294,615 and 5,412,095. This letter was received by Abbott Laboratories' Legal Division with a dated stamp of November 1, 1995 (page No. 35 of this addendum).

Subsequently, Invamed Inc. was sued by Abbott Laboratories regarding Patent 5,412,095 under legal case 95C 7185. Please note that Invamed has already submitted documents covering settlement of legal case 95C 7185 in their documents submitted to the FDA on December 14, 1996.

Sincerely

M. R. Patel.

Mahendra Patel, Ph.D.
Vice President

invamed inc.
908-274-2400 Fax: 908-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

CONTROL DOCUMENT

October 12, 1996

NDA ORIG AMENDMENT

RECEIVED

OCT 15 1996

GENERIC DRUGS

Ms. Carol Holquist
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

Re: **TERAZOSIN HYDROCHLORIDE TABLETS, 1 mg, 2 mg, 5 mg and 10 mg**
ANDA # 74-657

Dear Ms. Holquist

I refer to your facsimile document dated September 26, 1996 with respect to our pending ANDA # 74-657.

As recommended, the firm is herewith submitting twelve (12) copies each of the final printed insert labeling and Patient Information leaflet for your review and approval.

Please do not hesitate to contact me if you need any further information.

Sincerely

Mahendra Patel, Ph.D.
Vice-President

invamed inc.
908-274-2400 Fax: 908-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

CONTROL DOCUMENT

September 25, 1996

NEW CORRESP
NC

RECEIVED
SEP 2 5 1996
GENERIC DRUGS

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

Re: **TERAZOSIN HYDROCHLORIDE TABLETS, 1 mg, 2 mg, 5 mg and 10 mg**
ANDA # 74-657

Dear Sirs

Please note that a response to Minor Deficiencies was submitted towards the pending ANDA on 07/15/96. The method validation samples were submitted on 08/12/96 to Philadelphia laboratory.

We are requesting you to look into this matter and provide us the status information.

Sincerely

M R Patel.

Mahendra Patel, Ph.D.
Vice-President

invamed inc.
908-274-2400 Fax: 908-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

CONTROL DOCUMENT

September 6, 1996

NDA ORIG AMENDMENT
N/A

RECEIVED
SEP 09 1996
GENERIC DRUGS

Ms. Carol Holquist
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

Re: **TERAZOSIN HYDROCHLORIDE TABLETS, 1 mg, 2 mg, 5 mg and 10 mg**
ANDA # 74-657

Dear Ms. Holquist

I refer to your facsimile document dated August 26, 1996 with respect to our pending ANDA # 74-657.

As recommended, the firm is herewith submitting twelve (12) copies each of the final printed Patient Information leaflet for your review and approval.

We acknowledge your comment regarding the insert labeling. The firm will implement the recommended revision at the time of next printing.

Please do not hesitate to contact me if you need any further information.

Sincerely

M. Patel

Mahendra Patel, Ph.D.
Vice-President

invamed inc.
908-274-2400 Fax: 908-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

CONTROL DOCUMENT

August 26, 1996

Ms. Carol Holquist
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

Re: **TERAZOSIN HYDROCHLORIDE TABLETS, 1 mg, 2 mg, 5 mg and 10 mg**
ANDA # 74-657

Dear Ms. Holquist

I refer to your facsimile document dated August 26, 1996 with respect to our pending ANDA # 74-657. Regarding the mentioned labeling deficiencies it is our position that the Patient Information Insert should not be required for Terazosin Hydrochloride Tablets. The labeling of Hytrin Tablets does not include any language with respect to the availability of Patient Information Insert. Additionally, please note that the Hytrin Tablets (NDA 19057) now are again relisted in the Approved Drug Products List, Cumulative Supplement No.6 I have herewith provided a copy of page # 34 confirming the relisting.

Please do not hesitate to contact me if you need any further information.

Sincerely

Mahendra Patel, Ph.D.
Vice-President

invamed inc.
908-274-2400 Fax: 908-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

August 12, 1996

NDA ORIG AMENDMENT

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

RECEIVED
AUG 13 1996
GENERIC DRUGS

Re: **Terazosin Tablets, 1, 2, 5 and 10 mg**
ANDA # 74-657
Telephone Amendment

Dear Sirs

I have herewith enclosed a "***Telephone Amendment***" document to our pending application for **TERAZOSIN TABLETS, 1, 2, 5 and 10 mg (ANDA # 74-657)** as required under 21 CFR 314.120 (submitted in duplicate).

As recommended by Mr. Mike Smella, the firm has tightened the specifications for the total Impurities in the drug product from NMT % to NMT %. Attached please find a copy of the amended Product Specification and Release Report(s) and Stability Protocol(s) for each of the strength.

Please also note that as requested by the Philadelphia District, the method validation samples are sent to Mr. Falcone's attention by Federal Express. Attached please find a copy of cover letter addressed to Mr. Nicholas Falcone.

The firm has submitted an additional copy of this amendment to the U.S. Food and Drug Administration, New Jersey District Office. We hereby certify that this additional copy (field copy) is a true copy of the Archival and Review copies of the amendment.

Sincerely

M. C. Patel

Mahendra Patel, Ph.D.
Vice-President

invamed inc.

908-274-2400 Fax: 908-274-8989

2400 Rt. 130 North, Dayton, New Jersey 08810

ORIG AMENDMENT

July 15, 1996

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

ORIG AMENDMENT

Re: Terazosin Tablets, 1, 2, 5 and 10 mg
ANDA # 74-657
Minor Amendment

Dear Sirs

I have herewith enclosed a "*Minor Amendment*" document to our pending application for **TERAZOSIN TABLETS, 1, 2, 5 and 10 mg (ANDA # 74-657)** as required under 21 CFR 314.120 (submitted in duplicate).

The firm has submitted an additional copy of this amendment to the U.S. Food and Drug Administration, Newark District Office. We hereby certify that this additional copy (field copy) is a true copy of the Archival and Review copies of the amendment.

Sincerely

Mahendra Patel, Ph.D.
Vice-President

RECEIVED

JUL 16 1996

GENERIC DRUGS

invamed inc.
908-274-2400 Fax: 908-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

April 12, 1996

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

Re: TERAZOSIN HYDROCHLORIDE TABLETS, 1 mg, 2 mg, 5 mg and 10 mg
ANDA # 74-657
NEW INFORMATION

Dear Sirs

I have herewith enclosed a "*New Information*" document to our pending application for TERAZOSIN HYDROCHLORIDE TABLETS, 1 mg, 2 mg, 5 mg and 10 mg (ANDA # 74-657) as required under 21 CFR 314.120 (submitted in duplicate).

Please note that the proposed particle size specification for TERAZOSIN HYDROCHLORIDE was assigned based on only one lot evaluation. The firm has characterized three more lot samples of TERAZOSIN HYDROCHLORIDE as supplied by and based on the statistical analysis of all these lots the firm is requesting to amend the specification for % particle (by volume) value to be μm.

Attached please find an amended copy of the proposed Raw Material Release Report along with statistical analysis of particle size distribution.

I trust that the information submitted herein meets with your approval.

Sincerely

Mahendra Patel, Ph.D.
Vice-President

Unimed inc.
908-274-2400 Fax: 908-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

Conversion to minor denied.
Refer to TCon. HSmela 2/1/96

December 21, 1995

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

AMENDMENT
MAC

RECEIVED
DEC 22 1995
GENERIC DRUGS

Re: TERAZOSIN HYDROCHLORIDE TABLETS, 1 mg, 2 mg, 5 mg and 10 mg
ANDA # 74-657
Major Amendment with a request to be considered as a Minor Amendment

Dear Sirs

I have herewith enclosed a "*Major Amendment*" document to our pending application for TERAZOSIN HYDROCHLORIDE TABLETS, 1 mg, 2 mg, 5 mg and 10 mg (ANDA # 74-657) as required under 21 CFR 314.120 (submitted in duplicate).

Based on the review and the nature of this amendment as well as the reasons depicted below, we would like to request the OGD to consider this as a "*MINOR AMENDMENT*" and review accordingly:

Chemistry Deficiency 1: was merely an editorial correction requiring clarification. This comment does not constitute the amendment to be classified as a major amendment.

Chemistry Deficiency 2: was merely requiring a comparative scan for the reference/test product. In firm's opinion, this comment does not constitute the amendment to be classified as a major amendment.

Chemistry Deficiency 3: The first half of this comment was merely a recommendation. The acceptance of the recommendation by the firm does not require additional review time. The response to the other half of this comment was already a part of the original submission [Page(s) 1975 through 1995].

Chemistry Deficiency 4: was merely a recommendation. The acceptance of the recommendation by the firm does not require additional review time.

Yours Sincerely
Paulraj

Chemistry Deficiency 5: was merely a recommendation. The acceptance of the recommendation by the firm does not require additional review time.

Chemistry Deficiency 6: The referenced firms do not hold a Drug Master File.

Chemistry Deficiency 7: A closure liner does not require testing to be performed under USP <661>. The firm had submitted liner integrity data by providing USP <671> test results.

Chemistry Deficiency 9: was merely a recommendation. The acceptance of the recommendation by the firm does not require additional review time.

Chemistry Deficiency 10: was merely a recommendation. The acceptance of the recommendation by the firm does not require additional review time.

The firm has submitted an additional copy of this amendment to the U.S. Food and Drug Administration, Newark District Office. We hereby certify that this additional copy (field copy) is a true copy of the Archival and Review copies of the amendment.

Sincerely,

M. P. Patel

Mahendra Patel, Ph.D.
Vice-President

ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-3500

December 8, 1995

NEW CORRESP

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
7500 Standish Place, Rm. 150
Rockville, Maryland 20855

RE: Abbott Laboratories v. Invamed, Inc.;
Invamed, Inc. ANDA 74-657

Gentlemen:

ANDA 74-657 filed by Invamed, Inc. ("Invamed") contains certifications under 21 U.S.C. §355(j)(2)(A)(vii)(IV) asserting that the manufacture, use and sale of terazosin hydrochloride tablets (1,2,5, and 10mg generic versions of HYTRIN®) does not infringe two United States patents owned by Abbott Laboratories ("Abbott"). Specifically, the certifications are as to U.S. Patent Nos. 5,294,615 and 5,412,095. Notice of these certifications was received by Abbott on November 1, 1995.

This letter is to advise FDA that on December 7, 1995, Abbott filed a lawsuit against Invamed in federal district court in Chicago, Illinois, alleging infringement of the 5,412,095 patent. A copy of the lawsuit (No. 95C 7185, N.D. Ill.) is enclosed.

Because Abbott has filed its action within 45 days of receipt of notice of the certification, pursuant to the Federal Food, Drug and Cosmetic Act, §505(j)(4)(B)(iii), **the agency cannot approve ANDA 74-657 until "the expiration of the thirty-month period beginning on the date of the receipt of the notice...**or such shorter or longer period as the court may order..."

Should you have any questions concerning this matter, please feel free to contact me directly.

Sincerely,
ABBOTT LABORATORIES

Marilou Reed

Marilou Reed
Associate Director, Regulatory Affairs
D-491, AP6B/1
(708) 937-6844

cc: Division of Cardio-Renal Drug Products, HFD-110

RECEIVED
DEC 11 1995
GENERIC DRUGS

invamed inc.
908-274-2400 Fax: 908-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

July 11, 1995

NEW CORRESP

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

Re: **TERAZOSIN HYDROCHLORIDE TABLETS**
(1 mg, 2 mg, 5 mg and 10 mg strengths)
ANDA # 74-657
New Information

Dear Sirs

Please be advised that on June 16, 1995, Abbott Laboratories filed a complaint for patent infringement under 35 U.S.C. § 271(e)(2)(a) based upon Invamed's filing of its Abbreviated New Drug Application (ANDA) for its form of Terazosin Hydrochloride.

The patent infringement allegations are based on Abbott's **U.S. Patent Nos. 4,251,532** to Roteman, **5,294,615** to Meyer et al and **5,412,095** to Marley et al.

Invamed plans to defend itself against the allegations and is convinced it will succeed in proving non-infringement by its product. Invamed will keep the FDA apprised of any developments in this case as it proceeds.

Sincerely,

M. D. Patel

Mahendra Patel, Ph.D.
Vice President

RECEIVED

JUL 12 1995

GENERIC DRUGS

inc.
908-274-2400 Fax: 908-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

NEW CORRESP

May 3, 1995

Mr. William Russell, R.Ph.
Consumer Safety Officer
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

Re: **Response to telephonic inquiry**
TERAZOSIN HYDROCHLORIDE TABLETS
(1 mg, 2 mg, 5 mg and 10 mg strengths)
ANDA # 74-657

Dear Mr. Russell

As per our telephone conversation dated May 3, 1995, I am herewith submitting (in duplicate) page 2 of the PATENT CERTIFICATION (Section III) for your review and approval. Please note that the typo error has been corrected (4,251,532 instead of 4551532).

Sincerely,

Pankaj Dave, Ph.D.
Manager, Regulatory

RECEIVED
MAY 04 1995
GENERIC DRUGS

ORIGINAL

invamed inc.

908-274-2400 Fax: 908-274-8989

2400 Rt. 130 North, Dayton, New Jersey 08810

April 29, 1995

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

Re: **New Information**
TERAZOSIN HYDROCHLORIDE TABLETS
(1 mg, 2 mg, 5 mg and 10 mg strengths)
ANDA # 74-657

Dear Sirs:

As recommended I have herewith submitted an amended copy of **Section III, PATENT CERTIFICATION**, for your review and approval.

Sincerely,

M. R. Patel

Mahendra Patel, Ph.D.
Vice President

invamed inc.
908-274-2400 Fax: 908-274-8989
2400 Rt. 130 North, Dayton, New Jersey 08810

April 8, 1995

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855

Re: **Original ANDA Submission for**
TERAZOSIN HYDROCHLORIDE TABLETS
(1 mg, 2 mg, 5 mg and 10 mg strengths)

Dear Sirs:

I have herewith enclosed the original Abbreviated New Drug Application (ANDA) document for ***TERAZOSIN HYDROCHLORIDE TABLETS, 1 mg, 2 mg, 5 mg and 10 mg strengths.*** The ANDA application contains the following documents:

1.	Archival Copy	6 volumes
2.	Review Copy Chemistry, Manufacturing and Controls	3 volumes
3.	Review Copy Bioavailability/Bioequivalence (Hard copy of Raw Data with a copy of raw data on 5¼" disk, attached to the inner cover)	3 volumes

4. Two additional separately bound copies of **Section XV (Controls for the Finished Dosage Form)** and **Section XVI (Analytical Methods); Page(s) 2346 through 3383** as the drug substance and drug product are not compendial article(s).

The firm has submitted an additional copy of the Technical Section [as required under 314.50 (d) (1)] to the U.S. Food & Drug Administration, Newark District Office. We hereby certify that this additional copy (field copy) is a true copy of the Technical Section as described in § 314.94 (a) (9) contained in the Archival and Review copies of the abbreviated application.

Sincerely,

M. R. Patel.

Mahendra Patel, Ph.D.
Vice President