CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74446

ADMINISTRATIVE DOCUMENTS

Telecon

Date: 04/17/00

Control #: 00-144

Firm: Novopharm

Subject: Terazosin late filed patents

Participants: Gregg Davis, FDA and Jonathan Ng, Novopharm

Phone #: 905-642-4550, ext. 7030

Agenda:

I called Jonathan to discuss the two questions raised in his control document. The first question asked whether Novopharm can withdraw their paragraph IV certifications for the '176 and '615 patents. I stated that this would be acceptable as their application was acknowledged prior to Abbott listing their late filed patents in the Orange Book. As stated in 21 CFR 314.94(a)(12)(viii), if an applicant with a pending application voluntarily makes a patent certification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent.

The second question asked whether the Agency will entertain and grant another 180 day generic exclusivity for terazosin tablets. I stated that that the Agency will not discuss pending regulatory issues however, if Novopharm feels that they are ready for full approval after the withdrawal of the above listed patents, they should submit their final amendment requesting full approval of their application.

Jonathan agreed that this telecon would close this control document.

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

Date of Review: March 11, 1996

Date of Submission: February 29, 1996

Primary Reviewer: Carol Zimmermann

Secondary Reviewer: John Grace

ANDA Number: 74-446 **Review Cycle: 4 - FPL**

Applicant's Name [as seen on 356(h)]: Novopharm Limited

Manufacturer's Name (If different than applicant): Same

Established name: Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg.

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: December 21, 1994 (100s and 500s)- 1 mg, 2 mg, 5 mg and 10 mg. December 21, 1994 (1000s) - 2 mg, 5 mg and 10 mg. September 28, 1995 (1000s)- 1 mg.

Unit Dose Blister Label: February 29, 1996 (1 mg, 2 mg, 5 mg, 10 mg)

Unit Dose Carton Label: February 29, 1996 (100s - 1 mg, 2 mg, 5 mg and 10 mg)

Professional Package Insert Labeling: February 29, 1996 (Rev. September 1995).

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Hytrin

NDA Number: 19-057

NDA Drug Name: Hytrin Tablets

NDA Firm: Abbott Laboratories

Date of Approval of NDA Insert and supplement #:
September 14, 1994 - S-008.

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance?
No

Basis of Approval for the Container Labels:

Basis of Approval for the Carton Labeling:

Other Comments:

FOR THE RECORD:

1. Model for insert is Hytrin (Abbott, revised 7/94, approved 9/14/94).

2. Hytrin is covered by 5 patents. One patent expired on 5/31/94. Another relates to the dihydrate form and expires 2/17/00. Novopharm claims their product (anhydrous) will not infringe this patent. One other patent relating to the use of terazosin hydrochloride in the treatment of hypertension expires 1/21/97 and another relating to the anhydrous polymorphic form expires 4/29/13. The two other patents refer to the use of stereo specific isomer in hypertension or BPH. Exclusivity for the treatment of BPH expires 9/29/96. Exclusivity info has been "carved out" of the package

insert. Novopharm is challenging Abbott's patent relating to the use of terazosin hydrochloride in the treatment of hypertension patent. The patent was to expire on September 5, 1995. It was extended by GATT until January 21, 1997. If Novopharm gets full approval after 9/26/96, the labeling will need to be revised to include "BPH info".

3. The listed drug, Hytrin, starts with the dihydrate form of the drug. The generic firms are proposing a product starting with an anhydrous form, claiming this does not infringe on the patent which expires 2/17/00.

4. OGD accepted the application for review based on previous actions that show we do not consider water of hydration a factor in determining generic equivalence.

5. Storage -

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

NDA - Store below 86°F(30°C)

6. Novopharm has dropped from the chemical name and revised the structural formula to delete in the DESCRIPTION section. This is acceptable. It was decided by JGRACE, YMille, and JPhillips NOT to have generic firms, who use the indicate the tablets were [i.e., Each tablet contains terazosin hydrochloride .], since the form is and becomes during the process.

7. This product is not covered by a USP monograph. The USP - DI calls the product by the established name -

Terazosin Hydrochloride Tablets

8. The unit dose blisters are not light resistant. We will require Novopharm to have "Protect from light" on their cartons as does Abbott's Hytrin (RLD). John Grace discussed this with the chemist, S. Sherken, and he believes that, at minimum, this should be on the carton labeling.

Furthermore, John Grace discussed this with HFD-110 chemist, Bob Wolters, and was told that Abbott, as a condition of approval, was required to commit to developing a light-resistant package post-approval.

Hytrin tablets were subsequently withdrawn from the market and replace with Hytrin capsules. JPhillips and JGrace discussed this and it was decided to require the same of Novopharm.

9. Both Hytrin and Novopharm's tablets are unscored.

10. Product Line

The NDA markets this product in bottles of 100. The generic intends to market this product in bottles of 100, 500 and 1000 and unit-dose blister packs of 100.

11. This firm will differentiate the product strengths in the following manner:

1 mg - reverse box with green background
2 mg - reverse box in green with white background
5 mg - green
10 mg - black

/S/ 3-12-96
Primary Reviewer Date

/S/ 3-12-96
Chief, Labeling Rev. Branch Date

/S/ 4/30/96
/S/

cc:
ANDA 74-446
Dup/Division File
HFD-613/CZimmermann/JGrace (no cc)
njg/3/12/96/firmsnz\novophar\ltrs&rev\74446AP.L
Review
Final

M E M O R A N D U M

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

DATE: January 7, 1994 /S/ 1/7/94

FROM: Cecelia Parise
Consumer Safety Officer
Program Support Staff
Office of Generic Drugs

SUBJECT: ANDA 74-446, Novopharm
Terazosin

TO: The Record

Abbott hold two applications for Terazosin 19-057 and 20-223, the approved labeling for both applications lists hypertension, and benign prostatic hyperplasia. The Orange Book currently lists the exclusivity for benign prostatic hyperplasia (I-96) for the 20-223 application only. This will be corrected in the November supplement of the Orange Book.

Novopharm submitted their application referencing Abbott's 19-057 application which did not have the exclusivity for benign prostatic hyperplasia listed. They did not include the indication in their draft labeling but did not offer an explanation as to why it was excluded.

Since the Agency did not list the exclusivity for 19-057 it was decided after discussion with Gordon Johnston that we would not refuse to file the application. We would call the firm and ask them to revise their exclusivity statement after the November supplement of the Orange Book published.

I phoned Terry Ast, (212) 439-6400, agent for Novopharm and explained the issue surrounding the exclusivity for benign prostatic hyperplasia. I requested that the exclusivity statement for the application be revised after the publication of the November supplement to the Orange Book. Novopharm should provide a statment that exclusivity exists for this indication and that they will not include the indication in their labeling until after the expiration of the exclusivity. Terry Ast will advise Novopharm to revise their exclusivity statement.

The Orange Book does not cite exclusivity for both NDAs. Since the indication was omitted from the ANDA applicants labeling, and because 2 NDAs exist by the same applicant, for the same product, strength, etc. Novopharm appeared to address exclusivity as it is reflected in the Orange Book. Advise to follow plan noted by C. Parise. /S/ 1/7/94

M E M O R A N D U M

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

DATE: January 6, 1994

FROM: Khyati Roberts, CSO /S/ 1-7-94

SUBJECT: Terazosin Tablets

TO: The Record

I called HFD-110 regarding the approval of a new application for Hytrin Tablets and spoke with Kathleen Bongiovanni, CSO.

I asked Kathleen why there were two separate applications (20-223 and 19-057) for the same drug product with the same indications.

Kathleen was unsure of the history because she was not the CSO assigned to terazosin, but said she would check into the matter.

Kathleen said both applications were approved for HTN and BPH. She was not positive, but said it appeared as if Abbott submitted a new NDA rather than a supplement to their existing NDA so that the new indication, BPH, would be approved faster. Abbott was told that the Agency did not want two separate inserts for the same product so they should submit a supplement to the existing NDA for the new indication. Both the supplement and the new NDA would then be approved simultaneously.

Kathleen said she would have Zelda McDonald, CSO, call me back next week with further information since Zelda was the CSO handling terazosin.

File in ANDA

RECORD OF TELEPHONE CONVERSATION

DATE:10-20-95

PRODUCT NAME: Terazosin Tablets 1 mg, 2 mg, 5 mg & 10 mg.

ANDA/AADA NUMBER: 74-446

FIRM NAME: Novopharm Limited
Stouffville, Ontario, Canada L4A 1H5

NAME AND TITLE OF PERSON WITH
WHOM CONVERSATION WAS HELD:

Dr. Dietrich Bartel, Manager, U.S. Regulatory Affairs Pre-Approval, Novopharm
Mr. Stephen Sherken, Review Chemist, OGD, FDA
Ms. Sheila M. O'Keefe, OGD, FDA

PARTICIPANT(S) TELEPHONE:

Novopharm 1-800-361-3313

MINUTES OF CONVERSATION:

I received a phone call from Dr. Bartel at about 3 pm on October 20, 1995.

I told him that we had a problem with their response to question 5 that was in their minor ANDA amendment dated September 28, 1995. This question had to do with how they test, report and document analytical results of samples placed on stability, that are found to be out of limits.

I told Dr. Bartle that an <u>average</u> result that was within a given specification, could not be used to declare the sample to be within a specification, if one result was found to be outside of a specification.

I said that it is our feeling that any result falling outside of an established specification should be investigated and reported to the ANDA before a decision is made that the average of the results can be used to find the sample within the specification. In every case Novopharm should first establish the reason or cause for the failure before proceeding to a decision with any given sample.

Dr. Bartel said that he understood our concern and would amend their response to question 5, in an addendum to the ANDA. I told him that he should send their response to the ANDA (by mail) and in addition, FAX it to our office ASAP. At that point Ms. O'Keefe provided Dr. Bartel with our FAX number.

I then asked Mr. Bartel if he knew of the current status of the method validation sample, since the methods of all non-USP drugs must be validated by a FDA laboratory before the application can be approved. He said that he didn't know its exact status, since some one else at the firm has the responsibly to see that the samples and methods are provided to an FDA inspector for method validation.

He then said that he will try to obtain the information for me as soon as he could.

I then told him that I appreciated his call and the responses he gave me. At that point the tel-com ended.

/S/

Stephen Sherken

11/2/95

October 20, 1995

/S/

Sheila M. O'Keefe

11/6/95

DIVISION/BRANCH:

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

Date of Review: November 5, 1996

Date of Submission: October 30, 1996

Reviewer: Carol Holquist

ANDA Number: 74-446 **Review Cycle:** 5 - FPL

Applicant's Name [as seen on 356(h)]: Novopharm Limited

Manufacturer's Name (If different than applicant): Same

Established name: Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg.

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE CHEMISTRY COMMENTS TO THE FIRM:

B. LABELING DEFICIENCIES

1. INSERT

Physician Insert:

a. CLINICAL PHARMACOLOGY, Last table - Insert a space between "mm" and "Hg" and Revise to read "± 0.1" rather than ± under Mean Change, first entry.

b. PRECAUTIONS

i. General, Prostatic Cancer - Correct the spelling of "therapy" in the last sentence.

ii. Drug Interactions - Revise the subsection heading to read "Interactions" rather than "Interaction".

c. ADVERSE REACTIONS

i. Table 2 - Delete the extra space between "Respiratory System" and "Special Senses".

ii. Table 4 - Revise to read "Metabolic And Nutritional Disorders" rather than "Metabolic/Nutritional Disorders".

d. DOSAGE AND ADMINISTRATION

Subsequent Doses

Revise the last sentence to read:

There are insufficient data to support the use...

Please revise your 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.

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: December 21, 1994 (100s and 500s)- 1 mg, 2 mg, 5 mg and 10 mg. December 21, 1994 (1000s) - 2 mg, 5 mg and 10 mg. September 28, 1995 (1000s)- 1 mg.

Unit Dose Blister Label: February 29, 1996 (1 mg, 2 mg, 5 mg, 10 mg).

Unit Dose Carton Label: February 29, 1996 (100s - 1 mg, 2 mg, 5 mg and 10 mg).

Professional Package Insert Labeling:

Patient Information Insert:
October 30, 1996 (Rev. October 1996).

Revisions needed post-approval:

The following revisions are minor editorial and can be made post approval:

Patient Insert

a. Increase the prominence of the heading on the insert.

b. Other important facts about terazosin for BPH - Delete the space between the first and second entry.

c. Revise the temperature storage recommendations to read the same as the container and insert.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-057

NDA Drug Name: Hytrin Tablets

NDA Firm: Abbott Laboratories

Date of Approval of NDA Insert and supplement #: September 18, 1996/S-011

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Approved labels in file folder and side-by-side submission.

Basis of Approval for the Carton Labeling: Approved labeling in file folder and side-by-side submission.

FOR THE RECORD:

1. Model for insert is Hytrin (Abbott, revised 8/96, approved 9/18/96).

2. Hytrin is covered by 5 patents. One patent expired on 5/31/94. Another relates to the dihydrate form and expires 2/17/00. Novopharm claims their product (anhydrous) will not infringe this patent. One other patent relating to the use of terazosin hydrochloride in the treatment of hypertension expires 1/21/97 and another relating to the anhydrous polymorphic form expires 4/29/13. The two other patents refer to the use of stereo specific isomer in hypertension or BPH. Exclusivity for the treatment of BPH expired 9/29/96. Novopharm is challenging Abbott's patent relating to the use of terazosin hydrochloride in the treatment of

hypertension patent. The patent was to expire on September 5, 1995. It was extended by GATT until January 21, 1997.

3. The listed drug, Hytrin, starts with the dihydrate form of the drug. The generic firms are proposing a product starting with an anhydrous form, claiming this does not infringe on the patent which expires 2/17/00.

4. OGD accepted the application for review based on previous actions that show we do not consider water of hydration a factor in determining generic equivalence.

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

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7. This product is not covered by a USP monograph. The USP - DI calls the product by the established name -

Terazosin Hydrochloride Tablets

8. The unit dose blisters are not light resistant. We will require Novopharm to have "Protect from light" on their cartons as does Abbott's Hytrin (RLD). John Grace discussed this with the chemist, S. Sherken, and he believes that, at minimum, this should be on the carton labeling.

Furthermore, John Grace discussed this with HFD-110 chemist, Bob Wolters, and was told that Abbott, as a condition of approval, was required to commit to developing a light-resistant package post-approval. Hytrin tablets were subsequently withdrawn from the market and replace with Hytrin capsules. JPhillips and JGrace discussed this and it was decided to require the same of Novopharm.

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The NDA markets this product in bottles of 100. The generic intends to market this product in bottles of 100, 500 and 1000 and unit-dose blister packs of 100.

11. This firm will differentiate the product strengths in the following manner:

    1 mg - reverse box with green background .
    2 mg - reverse box in green with white background
    5 mg - green
    10 mg - black

12. This amendment was for the inclusion of the BPH information since the exclusivity expired on 9/26/96. I have contacted the firm via telephone on 11/6/96 to inform them of the labeling deficiencies. The patient package insert had a few deficiencies that were very minor and editorial. I chose not to tell the firm about these because they can be revised post approval.

Primary Reviewer — Date

/S/ — 11/8/96

Secondary Reviewer — Date

/S/ — 11/12/96

Team Leader, Labeling Review Branch — Date

cc:

ANDA 74-446
Dup/Division File
HFD-613/CHolquist/AVezza/JGrace (no cc)
njg/11/08/96/firmsnz\novophar\ltrs&rev\74446NA5.L
Review
Final

File 74-446

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Analysis
1114 Market Street, Room 1002
St. Louis, MO 63101
Tel (314) 539-2168
FAX Tel (314) 539-2113

Date: March 12, 1996

From: Henry D. Drew, Ph.D., Deputy Director, Chemistry II (HFD-920)

Subject: **Evaluation of ANDA - MVP for Terazosin Hydrochloride Drug Substance and Tablets (ANDA: 74-446) Submitted by Novopharm, Ltd., Toronto, Canada**

To: Stephen Sherken, OGD Review Chemist (HFD-625)

The evaluation of the Terazosin Hydrochloride Drug Substance and Tablets ANDA - MVP has been completed and all methods are acceptable for quality control and regulatory purposes. Please refer to specific comments from the evaluating chemist, James F. Brower, presented on the attached memorandum and worksheets.

As per program requirements, we are forwarding the original worksheets. We shall **retain the reserve sample for 90-days before disposal of remaining sample**. If you feel that the reserve sample should be held longer, please contact DDA.

/S/

Henry D. Drew, Ph.D.
Deputy Director, Chemistry II