

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74446

CORRESPONDENCE

Therese M. Ast, Ph.D., Esq.
Agent for: Novopharm, Ltd.
176 East 71st Street
New York, NY 10021

JUN 22 1994

Dear Madam:

This is in reference to your abbreviated new drug application dated December 16, 1993, 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.

Reference is also made to your amendments dated January 7, February 14, and March 14, 1994.

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

A. Chemistry Deficiencies:

1. Please include a test and specifications for individual and total degradants and impurities for the drug substance. Please identify and propose a specification for each major impurity.
2. Please test the drug substance for organic volatile impurities by the USP method. You may wish to contact your drug substance supplier for additional information.
3. Please add a melting point test for the drug substance and reference standard. Is there any difference in melting points when the drug substance is in the dihydrate or anhydrous form?
4. specification for water is %. Your reported result for batch 920507 was less than %. Please have update their COA specification for water to NMT %.
5. Please re-assay Lactose using the new monograph for Lactose Monohydrate NF and update your specifications. The monograph is found in the 9th supplement to the USP/NF, on page 3622.
6. Please re-assay Povidone using the latest USP methods and update your specifications. This includes the limit of aldehyde test, the k-value test and the test for nitrogen value. These tests are found in pages 3495-3496 of the 9th supplement.

7. Please justify why the four blends were not tested for blend assay and blend content uniformity. Please also justify why the tablets were not tested during the tableting runs for content uniformity (uniformity of dosage units). Please add in-process blend assay and in-process content uniformity (uniformity of dosage units) as routine controls.
8. The plastic material for the 500 mL bottle is identified on page 1983 as either
Shouldn't it be identified as
Please explain.
9. Please provide data and COAs from _____ and _____ showing that the rayon coil they supply will meet all the required USP specifications for _____
10. Please modify the system suitability test in the assay method used for the drug substance and drug product for uniformity of dosage units. Please include specifications for resolution (R), and column efficiency (number of theoretical plates, N). In order to determine resolution, a special system suitability solution should be used. It should contain a second compound that has a retention time (Rt) that is close, but baseline separated, from the terazosin peak and an equivalent absorbtivity to terazosin. It should also have the same tailing factor that terazosin has (k = _____. This special system suitability solution should not be used with either the standard or sample preparations.
11. Please determine the absolute sensitivity of the method.
12. Please add a second identification test for terazosin in the drug product. It should be specific. Tests such as IR or NMR are acceptable. Please provide a full description of the method and appropriate spectra from a standard and a representative sample.
13. Please add a test for water and a test for individual and total impurities as additional release tests for terazosin tablets. Please include a specification for each test. Please revise your COA and test protocols accordingly for each strength of product.
14. The validation data for the dissolution test is incomplete. Please provide data to show that the dissolution equipment meets the requirements of the USP's Apparatus Suitability Test in Section <721>.

15. Please add tests for water, and friability to your stability protocol. Please provide specifications for each test.
16. Please change the retesting schedule of all raw materials, regardless of whether the ingredient requires microbial testing, from 2 years to 1 year. You may, if you wish, provide two years of stability data to keep the retesting schedule at two years.
17. The DMF from is deficient. The holder is being notified.
18. Please provide proof from either the Canadian or other appropriate governmental entity that Novopharm is in compliance with the environmental laws of Canada and Ontario.

B. Labeling Deficiencies:

CONTAINER (100'S, 500'S, and 1000'S): Satisfactory in draft.

INSERT

1. DESCRIPTION

- a. Paragraph 2 (second sentence) -
 - (1) Each tablet, for oral administration, contains terazosin hydrochloride equivalent...
 - (2) Relocate "mg" to appear in conjunction with "1".
- b. In the list of inactive ingredients, change lactose to lactose monohydrate.
- c. Include the molecular formula: $C_{19}H_{25}N_5O_4 \cdot HCl$

2. CLINICAL PHARMACOLOGY

- a. Pharmacodynamics (paragraph 8)
...clinical trials
- b. Pharmacokinetics
 - (1) Final comment on this section is deferred until we have reviewed your bioequivalence data.

(2) Revise the first sentence to read:

...administered as tablets...

3. INDICATIONS AND USAGE, (second sentence)-

They can be used alone...

4. WARNINGS

a. Use "terazosin" rather than "terazosin hydrochloride" throughout this section [5 places].

b. ...first dose or first... (line 3)

5. PRECAUTIONS

a. Use "terazosin" rather than "terazosin hydrochloride" or "terazosin hydrochloride tablets" throughout this section [14 places].

b. line 3

occurred (spelling)

c. Carcinogenesis, Mutagenesis, Impairment of Fertility, Paragraph 4 (last sentence) -

This lesion has also been shown with prazosin hydrochloride...

d. Pregnancy:

Postpartum (non-hyphenated)

6. ADVERSE REACTIONS, paragraph 3 (last sentence) -

...following administration of terazosin.

7. OVERDOSAGE

Use "terazosin" rather than "terazosin hydrochloride" throughout this section [2 places].

8. DOSAGE AND ADMINISTRATION

Add the following to 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).

9. HOW SUPPLIED

- a. Indicate that the tablets are unscored.
- b. ...are available in four strengths:

Please revise your package insert labeling, then prepare and submit final printed container labels and draft insert labeling. We will not request final printed insert labeling until we have reviewed your bioequivalency data.

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. We require a satisfactory methods validation prior to approval of the ANDA. We will schedule validation once the testing issues are resolved.

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

Sincerely yours,

/S/ 6/21/94

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

ANDA 74-446

FEB 3 1994

Therese M. Ast, Ph.D., Esq.
U.S. Agent for: Novopharm, Ltd.
176 East 71st Street
New York, NY 10021

Dear Madam:

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

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

DATE OF APPLICATION: December 16, 1993

DATE OF RECEIPT: December 23, 1993

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

Although you have indicated that a third (field) copy of the application has been submitted, you have failed to certify that this copy is a "true" copy of the technical section of the application. Refer to sections 314.94(d)(5) and 314.440 of the Final Rule, published in the Federal Register, September 8, 1993, pages 47351 and 47352. Please promptly provide a revised third copy certification. Please clearly designate the submission as a "NEW CORRESPONDENCE".

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

Sincerely yours,

/S/

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Therese M. Ast, Ph.D., Esq.
Agent for: Novopharm, Ltd.
Granutec Inc.
4409 Airport Drive N.W.
Wilson, NC 27396

JUN 30 1995

Dear Madam:

This is in reference to your abbreviated new drug application dated December 16, 1993, 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 August 10, and December 21, 1994.

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

A. Chemistry Deficiencies:

1. Since both _____ are used in the _____ steps of terazosin hydrochloride, please test each lot of the drug substance for these solvents using _____ specifications.
2. Please include an additional specification for absorbtivity between the standard and sample for the ultraviolet (UV) identity test.
3. Please provide an Infrared scan of _____ and its standard. Please also provide thermal analysis scans of any high or low density _____ used in the unit-dose container. Please demonstrate that the unit-dose container or its outer box meets the USP requirement for Light Transmission.
4. Please provide matching multiple internal reflectance Infrared scans of the heat seal coating _____ and its standard.
5. Multiple assays at each test station for those lots placed on-stability are acceptable as long as all results are reported. If one result is out of limits, none of the results that are within limits, or the

average result, should be used to make a finding that the lot is passing stability.

6. Please explain how the sixteen 1000 count bottles were stored between the date the tablets were packaged into the bottles and the date the same tablets were repackaged into the unit dose containers.
7. DMF is deficient. The holder has been notified. Please confirm a response to our recent letter.

B. Labeling Deficiencies:

CONTAINER (100s, 500s, and 1000s): Satisfactory; however, you have not submitted final printed container labels for 1 mg tablets in bottles of 1000s as described in your HOW SUPPLIED section. Please submit these labels.

UNIT DOSE BLISTER: (draft)

The blister labels needs to reflect that the milligram strength is based on terazosin, not terazosin hydrochloride. We recommend -

_____ mg
(of terazosin)

UNIT DOSE CARTON (100s): (draft)

Include a statement as to whether or not the unit-dose package is child-resistant. If it is not child-resistant, we encourage the inclusion of a statement that if dispensed to outpatients, it should be with a child-resistant container, e.g.:

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

[NOTE: The second sentence is optional.]

INSERT:

1. WARNINGS

- a. Use "terazosin" rather than "terazosin tablets" throughout this section [5 places].
- b. Paragraph 2 (first sentence) -
decrease [spelling]

2. PRECAUTIONS

- a. 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.

b. 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)...

c. Pediatric Use

...in pediatric patients have not...

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

1. We require a satisfactory methods validation prior to approval of the ANDA. We are currently scheduling the validation study.
2. We believe that retest intervals for drug product ingredients should be no longer than one year unless supported with stability data. The acceptability of your retest program is a CGMP issue evaluated by the FDA investigator.

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/

6/29/95

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

cc: ANDA #74-446
DUP File
Division File
HFD-600/Reading File
Field Copy

Endorsements:

HFD-625/SSherken/6/9/95
HFD-625/DKönigstein/6/13/95 (on leave)
HFD-625/MSnela/6/12/95
HFD-613/JGrace/6/15/95
HFD-613/JPhillips/6/16/95
X:/wpfile/Carlos/Sherken/74446.LT2
F/T by: gp/6/16/95

/S/

6/23/95

/S/
6/23/95

/S/

6/22/95

NOT APPROVALE MINOR AMENDMENT

Novopharm Limited
Attention: Therese Ast, U.S. Agent
Granutec, Inc.
4409 Airport Drive, N.W.
Wilson, NC 27896

Dear Madam:

Reference is made to your abbreviated new drug application dated December 16, 1993, 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 September 28, November 2, December 19, 1995, February 29, and November 7, 1996.

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. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(4)(B)(iv) of the Act.

The listed drug product referenced in your application is subject to a period of patent protection which expires on April 29, 2013, (patent 5,504,207). However, you have informed us that litigation is underway in the United States District Court for the Northern District of Illinois, Eastern Division, involving a challenge to the patent (Abbott Laboratories, an Illinois Corporation, v. Novopharm Limited, a Corporation of the Dominion of Canada, Civil Action No. 96C 5868.) Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(4)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

*Added
1/27/96
Ruhle*

May 7, and June 17,

- b. the date of court decision [505(j)(4)(B)(iii) (I), (II), or (III)], which has been interpreted by the Agency to mean the date of the final order or judgement of that court from which no appeal can be or has been taken, or,
 - c. the patent has expired, and
2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the Agency whether circumstances have or have not arisen that may affect the effective date of final approval. Your amendment must provide:

1. 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, and
2.
 - a. updated information related to labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or
 - b. 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 effective final approval date is prohibited under Section 501 of the Act. Also, until the Agency issues the final approval letter, these drug products 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 Sheila M. O'Keefe, Consumer Safety Officer, at (301) 594-0370, for further instructions.

Sincerely yours,

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

cc:

ANDA 74-446
Division File
DUP Jacket
Field Copy
HFD-600/Reading File
HFD-8/P.Savino
HFD-610/JPhillips

Endorsements:

HFD-625/S.Sherken/3/13/96
HFD-625/MSmela/3/19/96
HFD-625/S.O'Keefe/3/27/96
HFD-613/C.Zimmermann/3/27/96
HFD-613/J.Grace/3/27/96

US/
4/12/96
4/12/96
for Smela
4.11.96
4/11/96

J. Phillips "b/ro"

TENTATIVE APPROVAL LETTER

DEC 29 1999

Novopharm NC Inc.
Attention: Dietrich Bartel
U.S. Agent for: Novopharm Limited
4700 Novopharm Blvd.
Wilson, NC 27893

Dear Sir:

This is in reference to your abbreviated new drug application dated December 16, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (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 to Novopharm Ltd. (Novopharm) on November 26, 1996, and to your amendments dated January 29, February 10, and September 3, 1999. Further reference is made to your undated correspondence pertaining to the resolution of Novopharm's patent litigation and received by this office on November 17, 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 (RLD) cited 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 patent] 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 Novopharm's favor upon issuance of the agency's initial tentative approval letter. Furthermore, Novopharm Limited made an additional 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 Novopharm Limited has complied with the requirements of Section 505(j)(2)(B) of the Act and that Abbott Laboratories initiated a patent infringement suit against Novopharm Limited in the United States District Court for the Northern District of Illinois - Eastern Division [Abbott Laboratories vs. Novopharm Limited, Civil Action No. 96C-5868 (N.D. III)]. You have also notified the agency that the U.S. district Court ruled in Novopharm's favor and that Abbott's appeal to the U.S. Court of Appeals for the Federal Circuit affirmed the lower court's decision on July 1, 1999. Your undated correspondence received by this office on November 17, 1999 summarizes these findings and concludes that the '207 patent no longer precludes approval of Novopharm's application for terazosin hydrochloride tablets.

However, we are unable to grant final approval for your application at this time. The district courts in both Inwood and Mova v. Shalala have 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. In light of these decisions, including the district court's order of June 1, 1998 in Mova, the agency will not enforce the "successful defense" provision of 21 C.F.R. 314.107(c)(1) and the related provision in 314.107(c)(4) which the courts found invalid.

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. That application, submitted by Geneva Pharmaceuticals, Inc. (Geneva) was subsequently approved by this office on December 31, 1998. As the first applicant to submit a substantially complete ANDA with a Paragraph IV Certification, Geneva is eligible for 180-days of market exclusivity for this drug product. Therefore, 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 been 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. This amendment also serves to reactivate this application prior to final approval and should be submitted even if none of these changes were made since the date of this second tentative approval letter. This amendment should be clearly designated 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" (the "Orange Book") list published by the agency.

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

Sincerely yours,

/S/

U

12/29/99

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



novopharm

Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5

Telephone (905) 642-4550
Fax (905) 642-4591

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855-2773

FACSIMILE AMENDMENT

NEW CORRESP

NC to
Fax

Subject: ANDA # 74-446
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

This Facsimile Amendment to our Abbreviated New Drug Application is in response to your facsimile dated August 6, 1999 from Dr. Rashmikant M. Patel, Ph.D. of the Division of Chemistry, which we received on August 9, 1999.

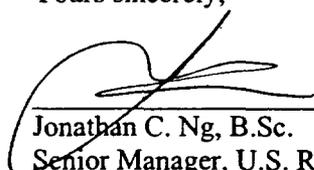
For the reviewers' convenience, each comment made by Dr. Patel has been restated in **bold** print and is followed by our response.

Enclosed are one (1) archival, one (1) review, and one (1) field copy of this amendment. We certify that the Field Copy is a true copy of the technical section contained in the Archival and Review copies of this application and has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions or comments with respect to this amendment, please direct all inquiries to the office of Jonathan Ng, Senior Manager, U.S. Regulatory Affairs, by telephone at 1-800-361-3313 or 416-291-8888, (ext. 7030), or by fax at 905-642-4590.

For written communications to be sent exclusively by mail or by courier, please direct correspondence to Dietrich Bartel, Director Regulatory Affairs, Novopharm N.C. Inc., 4700 Novopharm Blvd., Wilson, NC, U.S.A. 27893.

Yours sincerely,



Jonathan C. Ng, B.Sc.
Senior Manager, U.S. Regulatory Affairs
Novopharm Limited

SEP 03 1999

Date





novopharm

Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5

Telephone (905) 642-4550
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August 9, 1999

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place
Room 150
Rockville MD 20855-2773
U.S.A.

ACKNOWLEDGEMENT

~~NEW CORRESP~~
WC

SUBJECT: **ANDA # 74-446**
Terazosin Hydrochloride Tablets, 1, 2, 5 and 10 mg.

We thank you for your letter dated August 6, 1999 which we received on August 9, 1999 from Rashmikant M. Patel, Ph.D., Director, Division of Chemistry I, and Dale P. Conner, Pharm. D., Director, Division of Bioequivalence. We are presently addressing the comments listed and our responses will be forwarded promptly.

Should you have any further comments or questions, please do not hesitate to contact us directly at 1-800-361-3313 or 416-291-8888 ext. 7030.

Yours sincerely,

Jonathan Ng, B.Sc.
Manager, ANDA Approvals

*8/13/99 NAZ
Rushy*



*MW
8-11-99*



Novopharm

Stouffville, Ontario, Canada L4A 1H5

Telephone (905) 642-4550
Int'l Fax (905) 642-4591
Canadian & U.S. Fax (905) 642-4590

NDA ORIG AMENDMENT

N/A

Novopharm
Regulatory Affairs
U.S. Regulatory Administration
Control Room
North II (MPN II)
Crestwood Place, Room 150
Stouffville, ON
M9C 5R7
Tel: (905) 642-2773

MINOR AMENDMENT

ANDA # 74-446

Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

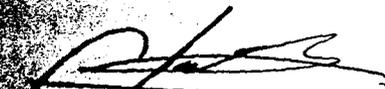
In this Minor Amendment to our abbreviated new drug application, we would like to withdraw the Paragraph IV Certifications that were filed for U.S. Patent No. 5,294,615 and U.S. Patent No. 5,212,176 due to the fact that these are "late-listed" patents. Consequently, we also request the final approval of our ANDA. There have been no further changes made to our ANDA since receiving tentative approval on December 29, 1999.

Enclosed are one (1) archival, one (1) review, and one (1) field copy of this amendment. We certify that the Field Copy is a true copy of the technical section contained in the Archival and Review copies of this application.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions or comments with respect to this amendment, please direct all inquiries to the office of Jonathan Ng, Senior Manager, U.S. Regulatory Affairs, by telephone at 1-800-361-3313 or 416-291-8888, (ext. 7030), or by fax at 905-642-4590.

For written communications to be sent exclusively by mail or by courier, please direct correspondence to Dietrich Bartel, Director Regulatory Affairs, Novopharm N.C. Inc., 4700 Novopharm Blvd., Wilson, NC, U.S.A. 27893.

Yours sincerely,


Jonathan C. Ng, B.Sc.
Senior Manager, U.S. Regulatory Affairs
Novopharm Limited

MAR 17 2000



Handwritten initials and date: JW 12-19-99





novopharm

Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5

Telephone (905) 642-4550
Fax (905) 642-4591

Office of Generic Drugs
Centre for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855-2773

AMENDMENT

NDA ORIG AMENDMENT

AC

SUBJECT: ANDA # 74-446
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg & 10 mg

Reference is made to our amendment dated January 29, 1999.

We are filing this Amendment to provide for an additional packaging size. Information and data to support this addition are included within this Amendment and in the Amendment submitted on January 29, 1999, including copies of the exhibit batches of Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg & 10 mg, manufactured using the drug substance supplied by

Enclosed are one (1) archival, one (1) review copy and one (1) field copy of this Amendment. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this Amendment to be evaluated. If there are any questions or comments with respect to this Amendment, please direct all inquiries to the office of Jonathan Ng, Manager, ANDA Approvals, by Telephone at 1-800-361-3313 or 905-642-4500, ext. 7030, or by fax at 905-642-4590.

For written communications to be sent exclusively by mail or by courier, please direct correspondence to Dietrich Bartel, Director Regulatory Affairs, Novopharm N.C. Inc., 4700 Novopharm Blvd., Wilson, NC, U.S.A. 27893.

Yours sincerely,

Jonathan Ng, B.Sc.
Manager, ANDA Approvals,
U.S. Regulatory Affairs
NOVOPHARM LIMITED

FEB 10 1999

Date

RECEIVED

FEB 11 1999

GENERIC DRUGS



Novopharm
30
1965-1995
Years of Caring





Novopharm Limited
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Office of Generic Drugs
Centre for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855-2773

AMENDMENT

NDA ORIG AMENDMENT

N/A/C

SUBJECT: ANDA # 74-446
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg & 10 mg

Pursuant to 21 CFR § 314.60 (b) (1) (v), we are filing this Amendment to our Abbreviated New Drug Application for Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg & 10 mg to provide for the use of an alternate drug substance manufacturer,

Information and data to support this change are included within this Amendment. Test batches of Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg & 10 mg have been manufactured to provide supporting data.

Also, in reference to the Agency's letter dated December 6, 1995, we had committed to develop a light-resistant packaging for this product in the minor amendment dated February 29, 1996. Information and data to support this commitment are included within this Amendment.

In addition, we hereby inform you that effective Aug. 3, 1998, Novopharm Limited has changed its U.S. Agent. Please note that a letter of authorization allowing Dietrich Bartel to act as our authorized U.S. responsible official is enclosed in the following pages.

Enclosed are one (1) archival, one (1) review copy and one (1) field copy of this Amendment. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this Amendment to be evaluated. If there are any questions or comments with respect to this Amendment, please direct all inquiries to the office of Jonathan Ng, Manager, ANDA Approvals, by Telephone at 1-800-361-3013 or 905-642-4500, ext. 7030, or by fax at 905-642-4590.

FEB 10 1998

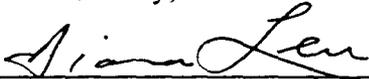


ANDA # 74-446

Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg & 10 mg

For written communications to be sent exclusively by mail or by courier, please direct correspondence to Dietrich Bartel, Director Regulatory Affairs, Novopharm N.C. Inc., 4700 Novopharm Blvd., Wilson, NC, U.S.A. 27893.

Yours sincerely,



for

Jonathan Ng, B.Sc.
Manager, ANDA Approvals,
U.S. Regulatory Affairs
NOVOPHARM LIMITED

JAN 29 1999

Date



ABBOTT

Pharmaceutical Products Division

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

NAE
Wich
10/7/98

September 28, 1998

NEW CORRESP
NO

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
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

Handwritten signature

ABBOTT

Pharmaceutical Products Division

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

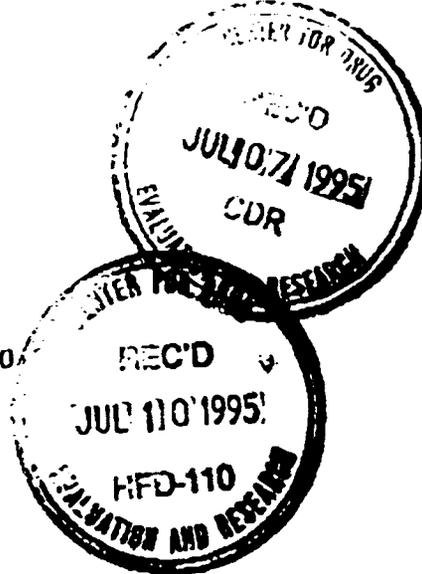
(YR)
SUPPL NEW CORRSP

NDA 19-057
HYTRIN (terazosin hydrochloride) TABLETS

NDA 20-347
HYTRIN (terazosin hydrochloride) CAPSULES

July 6, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Division of Cardio-Renal Drug Products, HFD-110
ATTN: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857



95 JUL -5 PM 3:34

Dear Sir or Madam:

Please refer to Abbott Laboratories' New Drug Applications for HYTRIN (terazosin hydrochloride) Tablets, NDA 19-057 and for HYTRIN (terazosin hydrochloride) Capsules, NDA 20-347.

The following information is submitted pursuant to 21 CFR 314.53(c)(1), in order to provide updated patent expiration information in accordance with our current analysis of the pertinent provision of the Uruguay Round Agreements Act.

<u>Patent #</u>	<u>Expiration Date</u>	<u>Topic of Patent</u>
4,026,894	May 31, 1994	The compound, terazosin, and its pharmaceutically-acceptable salts.
4,112,097	January 21, 1997	Pharmaceutical compositions comprising terazosin or one of its pharmaceutically acceptable salts.
4,251,532	February 17, 2000	The compound, terazosin hydrochloride dihydrate, and pharmaceutical compositions comprising terazosin hydrochloride dihydrate.
5,212,176	June 29, 2010	The R(+)-enantiomer of the compound, terazosin hydrochloride dihydrate, and its uses.

ORIGINAL

5,294,615

April 29, 2013

The compound, anhydrous terazosin hydrochloride Form II, pharmaceutical compositions and methods of treatment of hypertension, benign prostatic hyperplasia and congestive heart failure containing a therapeutically effective amount of terazosin hydrochloride Form II.

noted
RK
←

5,412,095

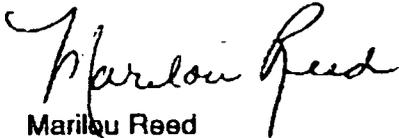
April 29, 2013

The compound anhydrous terazosin hydrochloride Form III and the compound terazosin hydrochloride methanolate.

The undersigned declares that Patent Nos. 4,026,894, 4,112,097, 4,251,532, 5,212,176 5,294,615 and 5,412,095 cover the formulation, composition and/or method of use of terazosin hydrochloride, the active ingredient in HYTRIN tablets and HYTRIN capsules. These products are currently approved under section 505 of the Federal Food, Drug and Cosmetic Act.

An original and a copy of this letter are being submitted.

Respectfully submitted,



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

CC: Central Document Room, CDER, FDA, Park Bldg., Rm., 214

Mary Ann Holovac
Division of Drug Information Resources
HFD-84, Rm 8B-37



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Office of Generic Drugs
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Food & Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855-2773

TELEPHONE CORRESPONDENCE

Attn.: Mr. Peter Rickman

SUBJECT: ANDA #74-446
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

This correspondence is in response to your telephone communication on August 13, 1996 to our U.S. agent, Dr. Thérèse M. Ast, concerning the consequence of the paragraph IV certification filed for U.S. Patent No. 4,251,532 expiring on February 17, 2000.

The paragraph IV patent certification for U.S. Patent No. 4,251,532 was filed on December 16, 1993, and notice to the patent holder and sponsor, Abbott Laboratories, was provided on February 24, 1994. A copy of the return receipt for the notice provided to Abbott Laboratories was submitted in our March 14, 1994 amendment to our ANDA for Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg. We note that the statutory period of 45 days has expired and that Abbott Laboratories has not instituted any civil suit against Novopharm Limited for U.S. Patent No. 4,251,532.

Should you have any further questions or comments, you may direct written and telephoned communications to Dr. Thérèse Ast at (919) 291-9100 or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

Dietrich Bartel
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Granutec Inc.
4409 Airport Drive N.W.
Wilson, N.C. 27896
Via PUROLATOR COURIER (Waybill # 286 915 9414)

AUG 16 1996

(date)

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AUG 16 1996
GENERIC DRUGS





novopharm

Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5

Telephone (905) 642-4550
Fax (905) 642-4591

Carol Holquist
Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855-2773

TELEPHONE AMENDMENT

SUBJECT: **ANDA #74-446**
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

Dear Ms. Holquist:

This Telephone Amendment to our abbreviated new drug application is in response to your telephone communication on September 26, 1996 to Ms. Diane Servello, concerning the addition of the benign prostatic hyperplasia (BPH) indication in the product insert labeling.

We have revised the physician insert labeling for terazosin hydrochloride tablets to include references to the BPH indication in accordance with the new approved labeling for HYTRIN® (approved: September 18, 1996). We have also prepared a patient information insert for terazosin hydrochloride tablets, and we are submitting twelve final printed physician inserts and patient information inserts in Exhibit I and II, respectively.

Enclosed are one (1) archival and one (1) review copy of this Amendment. Should you have any further questions or comments, you may direct written and telephoned communications to our US. Agent, Dr. Thérèse Ast, at (919) 291-9100, or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

Dietrich Bartel
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

OCT 30 1996

(date)

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Granutec Inc.
4409 Airport Drive N.W.
Wilson, N.C. 27896
Via PUROLATOR COURIER (Waybill # 286 915 9455)





ABBOTT

Pharmaceutical Products Division

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

September 13, 1996

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

RECEIVED

SEP 16 1996

GENERIC DRUGS

**RE: Abbott Laboratories v. NovoPharm Limited, and
NovoPharm Limited, ANDA 74-446**

NEW COPY

Gentlemen:

ANDA 74-446 filed by NovoPharm Limited ("Novopharm") 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® would not be prevented by a United States patent owned by Abbott Laboratories ("Abbott") because, according to NovoPharm, the patent is invalid. Specifically, the certification is to U.S. Patent No. 5,504,207. Notice of this certification was received by Abbott on August 12, 1996.

This letter is to advise FDA that on September 13, 1996, Abbott filed a lawsuit against NovoPharm in federal district court in Chicago, Illinois, alleging infringement of the above-referenced patent. A copy of the lawsuit is enclosed. [No. 96C 5868 (N.D. Ill. filed September 13, 1996).]

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 74-446 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

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

cc: Division of Cardio-Renal Drug Products, HFD-110
Central Document Room, Park Bldg., Rm. 2-14
Drug Information Services Branch, HFD-84



novopharm

Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5

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Fax (905) 642-4591

Peter Rickman
Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place
Room 150
Rockville, MD
U.S.A. 20855-2773

ANDA CORRESPONDENCE
NEW
MC

SUBJECT: **ANDA #74-446**
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

Dear Mr. Rickman:

This correspondence is in response to your telephone communication on October 23, 1996 to Mr. Dietrich Bartel, concerning the patent certification for U.S. Patent 5,504,207 expiring on April 29, 2013.

A paragraph IV patent certification for U.S. Patent No. 5,504,207 was filed on August 7, 1996, and notice to the patent holder and sponsor, Abbott Laboratories, was provided on August 12, 1996. A copy of the return receipt for the notice provided and a certification statement certifying that proper notice has been provided is included in Exhibit I and II, respectively. In response to the notification, Abbott Laboratories has initiated a civil suit against Novopharm Limited on September 18, 1996 (Civil Action # 96C 5868, Northern District of Illinois). The matter is still pending, and a trial date has not been set at this time.

Should you have any further questions or comments, you may direct written and telephoned communications to Dr. Thérèse Ast at (919) 291-9100 or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

Dietrich Bartel
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

OCT 23 1996

(date)

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Granotec Inc.
4409 Airport Drive N.W.
Wilson, N.C. 27896
Via PUROLATOR COURIER (Waybill # 286 915 9372)

RECEIVED

OCT 27 1996

GENERIC DRUGS





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Fax (905) 642-4591

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Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855-2773

MINOR AMENDMENT

RECEIVED

AUG 09 1996

GENERIC DRUGS

SUBJECT: ANDA #74-446
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

This amendment to our abbreviated new drug application is made pursuant to Section 505 (j) (2) (A) (vii) of the Federal Food, Drug and Cosmetic Act. We are amending our Paragraph IV Certification previously filed on August 6, 1996 for U.S. Patent 5,504,207 expiring on April 29, 2013, to include reference to patent invalidity. A copy of the revised Patent Certification Statement is included in Exhibit I for your review.

Enclosed are one (1) archival, one (1) review and one (1) field copy of this amendment. We certify that the field copy is a true copy of the technical section contained in the archival and review copies of this application.

Should you have any further questions or comments, you may direct written and telephoned communications to Dr. Thérèse Ast at (919) 291-9100 or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

Dietrich Bartel
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

AUG 07 1996

(date)

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Granutec Inc.
4409 Airport Drive N.W.
Wilson, N.C. 27896
Via PUROLATOR COURIER (Waybill # 328 180 3514)





novopharm

Novopharm Limited
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Fax (905) 642-4591

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855-2773

RECEIVED MINOR AMENDMENT

'AUG' 17 1996

GENERIC DRUGS

SUBJECT: **ANDA #74-446**
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

This amendment to our abbreviated new drug application is made pursuant to Section 505 (j) (2) (A) (vii) of the Federal Food, Drug and Cosmetic Act. We are amending our application to replace the Paragraph III Certification previously filed on June 16, 1996 with a Paragraph IV Certification for U.S. Patent 5,504,207 expiring on April 29, 2013. A copy of the required Patent Certification Statement is included in Exhibit I.

Enclosed are one (1) archival, one (1) review and one (1) field copy of this amendment. We certify that the field copy is a true copy of the technical section contained in the archival and review copies of this application.

Should you have any further questions or comments, you may direct written and telephoned communications to Dr. Thérèse Ast at (919) 291-9100 or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

Dietrich Bartel
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

AUG 06 1996

(date)

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Granotec Inc.
4409 Airport Drive N.W.
Wilson, N.C. 27896
Via PUROLATOR COURIER (Waybill # 327 236 8006)





novopharm

Novopharm Limited
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Telephone (905) 642-4550
Fax (905) 642-4591

NDA ORIG AMENDMENT

AF

MINOR AMENDMENT
RECEIVED

*EPL
Sent to file 10/2/95
CJ...
3-11-96*

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855-2773

MAR 01 1996

GENERAL DRUGS

SUBJECT: ANDA # 74-446
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

This **Minor Amendment** to our abbreviated new drug application is in response to your letter dated December 6, 1995 from the Division of Labeling and Program Support, which we received on December 8, 1995.

For the reviewers' convenience, each comment has been restated in **bold** print and is followed by our response. Enclosed are one (1) archival and one (1) review copy of this amendment.

Should you have any further questions or comments, you may direct written and telephoned communications to Dr. Thérèse Ast at (919) 291-9100 or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

Dietrich Bartel
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

FEB 29 1996

(date)

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Granutec Inc.
4409 Airport Drive N.W.
Wilson, N.C. 27896
Via PUROLATOR COURIER (Waybill # 286 915 5297)





ABBOTT

Pharmaceutical Products Division

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

February 2, 1996

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

NEW CORRESP

RECEIVED

FEB 05 1996

GENERIC DRUG

RE: **Abbott Laboratories v. NovoPharm Limited, and
NovoPharm Limited, ANDA 74-446**

Gentlemen:

ANDA 74-446 filed by NovoPharm Limited ("Novopharm") 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"). Specifically, the certification is to U.S. Patent No. 4,112,097. Notice of this certification was received by Abbott on December 26, 1995.

This letter is to advise FDA that on February 1, 1996, Abbott filed a lawsuit against NovoPharm in federal district court in Chicago, Illinois, alleging infringement of the above-referenced patents. A copy of the lawsuit is enclosed. [No. 96C 0611 (N.D. Ill. filed February 1, 1996).]

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 74-446 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
Associate Director, Regulatory Affairs
D-491, AP6B/1
(847) 937-6844

cc: Division of Cardio-Renal Drug Products, HFD-110
Central Document Room, Park Bldg., Rm. 2-14
Drug Information Services Branch, HFD-84



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Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855-2773

MINOR AMENDMENT
MINOR AMENDMENT

N/A

SUBJECT: ANDA #74-446
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

This amendment to our abbreviated new drug application is made pursuant to Section 505 (j) (2) (A) (vii) of the Federal Food, Drug and Cosmetic Act.

Enclosed are the required Patent Certification Statements (Exhibit I). A Paragraph IV Certification has been made for U.S. Patent 4,112,097 with respect to the expiration date of January 21, 1997, as published in Cumulative Supplement #8 of the Approved Drug Products, 15th Edition, which Novopharm Limited believes is incorrect. At this time, Novopharm is also submitting a Paragraph II Certification Statement for U.S. Patent 4,112,097 with respect to its correct expiration date of October 14, 1995. A request for confirmation of the correctness of the patent information has been made to the Drug Information Services Branch of the Food and Drug Administration in accordance with procedures under 21 CFR 314.53 (f). A copy of the correspondence is enclosed (Exhibit II). In addition, we are also filing a Paragraph IV Certification for U.S. Patent No. 5,412,095 expiring on April 29, 2013, U.S. Patent No. 5,212,176 expiring on June 29, 2010 and U.S. Patent No. 5,294,615 expiring on April 29, 2013.

We are also amending our abbreviated new drug application to include two tests for polymorphic form determination. A summary of supporting documents for the proposed addition is included in Exhibit III. Enclosed are one (1) archival, one (1) review and one (1) field copy of this amendment. We certify that the field copy is a true copy of the technical section contained in the archival and review copies of this application.

Should you have any further questions or comments, you may direct written and telephoned communications to Dr. Thérèse Ast at (919) 291-9100 or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

Dietrich Bartel

Dietrich Bartel
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Granutec Inc.
4409 Airport Drive N.W.

DEC 19 1995

(date)

RECEIVED

DEC 20 1995

GENERIC DRUGS

29 Dec 95
[Signature]





novopharm

Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5

Telephone (905) 642-4550
Fax (905) 642-4591

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855-2773

*Telephone Amendment -
Addendum to Minor Amendment*

NDA ORIG AMENDMENT

Attn: Mr. Steve Sherken, Reviewing Chemist

SUBJECT: **ANDA #74-446**
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

This addendum to the minor amendment to our ANDA for Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg, is in response to your telephone communication on October 20, 1995 concerning the reporting of multiple assays at each test station for stability testing.

We have amended our response to comment # 5 regarding the reporting of multiple assays at each test station for stability testing, and we acknowledge that all multiple assay test results for stability testing must be reported regardless whether each individual result meets test specification. We also acknowledge that all stability test results and test specifications for Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg are to be submitted in the annual reports for Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg. We note that FDA has not obtained Novopharm's finished product samples of Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg for validation studies.

Enclosed are one (1) archival, one (1) review and one (1) field copy of this addendum. We certify that the field copy is a true copy of the technical section contained in the archival and review copies of this application.

Should you have any further questions or comments, you may direct written and telephoned communications to our US. Agent, Dr. Thérèse Ast, at (919) 291-9100, or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

Dietrich Bartel
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

NOV 0 2 1995

(date)

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Granutec Inc.
4409 Airport Drive N.W.
Wilson, N.C. 27896
Via PUROLATOR COURIER (Waybill # 317 523 9759)

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GENERIC DRUGS



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novopharm

Novopharm Limited
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Telephone (905) 642-4550
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Ms. Carol Holquist
Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855-2773

TELEPHONE AMENDMENT

RECEIVED

NOV 08 1996

ORIG AMENDMENT

GENERIC DRUGS

SUBJECT: ANDA #74-446
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

Dear Ms. Holquist:

This Telephone Amendment to our abbreviated new drug application is in response to your telephone communication on November 6, 1996 to Mr. Jonathan Ng, concerning the revision of Novopharm's physician insert labeling for terazosin hydrochloride tablets.

We have revised the physician insert labeling for terazosin hydrochloride tablets in accordance to the new approved labeling for HYTRIN[®] (approved: September 18, 1996), and we are submitting twelve final printed physician inserts in Exhibit I for your review.

Enclosed are one (1) archival and one (1) review copy of this Amendment. Should you have any further questions or comments, you may direct written and telephoned communications to our US. Agent, Dr. Thérèse Ast, at (919) 291-9100, or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

Dietrich Bartel
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

NOV 07 1996

(date)

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Granutec Inc.
4409 Airport Drive N.W.
Wilson, N.C. 27896
Via PUROLATOR COURIER (Waybill # 286 915 9331)





novopharm

Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5

Noted Monday 8/14/95

Telephone (905) 642-4550
Fax (905) 642-4591

ORIGINAL FILE

NDA ORIG AMENDMENT

N/A

MINOR AMENDMENT

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855-2773

SUBJECT: **ANDA #74-446**
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

This **Minor Amendment** to our abbreviated new drug application is in response to your letter dated June 30, 1995 from the Division of Chemistry I, which we received on July 6, 1995.

For the reviewers' convenience, each comment has been restated in **bold** print and is followed by our response.

Enclosed are one (1) archival, one (1) review and one (1) field copy of this Amendment. We certify that the field copy is a true copy of the technical section contained in the archival and review copies of this application.

Should you have any further questions or comments, you may direct written and telephoned communications to our US. Agent, Dr. Thérèse Ast, at (919) 291-9100, or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

Dietrich Bartel

Dietrich Bartel
Manager, U.S. Regulatory Affairs Pre-Approval
NOVOPHARM LIMITED

SEP 28 1995

(date)

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
Granutec Inc.
4409 Airport Drive N.W.
Wilson, N.C. 27896
Via PUROLATOR COURIER (Waybill # 286 915 2575)

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SEP 28 1995

GENERIC DRUGS



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[Signature]



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Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5

Telephone (905) 642-4550
Fax (905) 642-4591

December 21, 1994

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855-2773

MAJOR AMENDMENT

NIA
AMENDMENT

SUBJECT: ANDA #74-446
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

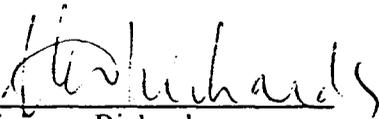
This Major Amendment to our abbreviated new drug application is in response to your letter dated June 22, 1994 from the Division of Chemistry I, which we received on June 27, 1994.

For the reviewers' convenience, each comment has been restated in **bold print** and is followed by our response. This constitutes **Part One** of this Amendment. We are including data to support a unit dose packaging format for this product in **Part Two** of this Amendment.

Enclosed are one (1) archival, one (1) review and one (1) field copy of this Amendment. We certify that the field copy is a true copy of the technical section contained in the archival and review copies of this application.

Should you have any further questions or comments, you may direct written and telephoned communications to our US. Agent, Dr. Thérèse Ast, at (919) 291-9100, or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,


Vivienne Richards
Director, U.S. Regulatory Affairs

DEC 21 1994

(Date)

Enclosures

cc: Dr. Thérèse Ast, Ph.D, Esq.,
Granotec Inc.,
4409 Airport Drive N.W.,
Wilson, NC 27896

Via Purolator (Waybill # 286 915 0173)

RECEIVED

DEC 22 1994

GENERIC DRUGS

William 95
Richardson



August 10, 1994

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8/20/94*

Mr. Douglas Sporn
Acting Director
Office of Generic Drugs, HFD-630
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, Maryland 20855
USA

MINOR AMENDMENT

MAE

Dear Mr. Sporn:

RE: **ANDA #74-446**
TERAZOSIN HYDROCHLORIDE TABLETS
1 mg, 2 mg, 5 mg and 10 mg

This letter is to inform you that effective August 15th, 1994, Novopharm's U.S. agent, Dr. Therese Ast, will be based at our subsidiary, Granutec Inc. at Wilson, North Carolina, where she will assume the position of V.P. Legal and Scientific Affairs for Granutec Inc.

Dr. Ast will continue to act as Agent for Novopharm Ltd., of Canada, and you may direct written and telephoned communications directly to her at the address below:

Therese M. Ast, Ph.D.,
Attorney-at-law,
Granutec Inc.,
4409 Airport Drive N.W.,
Wilson, N.C. 27396.

Telephone: (919) 291-9100
Fax: (919) 291-5817

You may also communicate directly with the undersigned at the address on this letterhead, should you choose to do so.

Yours sincerely,
Novopharm Ltd.,

D. Bartel

Dietrich Bartel
Manager, Pre-Approval Activities
U.S. Regulatory Affairs

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AUG 17 1994

GENERIC DRUGS





Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5

Telephone (905) 642-4550
Fax (905) 642-4591

June 28, 1994

NEW CORRESP

NE

Mr. Douglas L. Sporn
Acting Director
Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II (MPN II)
7500 Standish Place
Room 150
Rockville, MD
U.S.A. 20855-2773

Dear Mr. Sporn:

SUBJECT: ANDA 74-446
Terazosin Hydrochloride Tablets
1 mg, 2 mg, 5 mg and 10 mg

We thank you for your letter dated June 22, 1994 which we received on June 27, 1994 from Dr. Rashmikant M. Patel of the Division of Chemistry I. We are presently addressing the comments listed and our responses will be forwarded promptly.

Should you have any further comments or questions, please do not hesitate to contact us directly at 1-800-361-3313 or our U.S. Agent, Dr. Thérèse Ast at 1-212-439-9252 or 1-212-439-6400.

Yours sincerely,

Dietrich Bartel
Manager, Pre-Approval Activities
U.S. Regulatory Affairs

cc: Dr. Thérèse Ast (Attorney-at-Law, 176 East 71st Street, New York, NY 10021)

Via Purolator (Waybill # 303 491 3669)

RECEIVED

JUN 29 1994

GENERIC DRUGS

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novopharm

Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5

Telephone (905) 642-4550
Fax (905) 642-4591

Mr. Douglas L. Sporn
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855-2773

AMENDMENT

NEW CORRESP

NC

Dear Mr. Sporn:

Subject: **ANDA # 74-446**
Terazosin Hydrochloride Tablets
1 mg, 2 mg, 5 mg, and 10 mg

This amendment provides evidence as required by the FDA under Section 505 (j) (2) (B) (i) of the Federal Food, Drug, and Cosmetic Act to the sponsor or patent holder, in the form of a return receipt (Exhibit I) as required for our Paragraph IV Patent Certification.

We have also enclosed a certification statement that notice has been provided (Exhibit II) and copies of the notification to Abbott Laboratories dated February 24, 1994 (Exhibit III).

Enclosed are one (1) Archival Copy, one (1) Review Copy, and one (1) Field Copy of this Amendment. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this Amendment.

If there are any questions with respect to this amendment, you may direct written and telephoned communications to Dr. Thérèse Ast at (212) 439-6400 or (212) 439-9252, or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

Vivienne Richards
Vivienne Richards, B.Sc., M.A.
Director U.S. Regulatory Affairs
NOVOPHARM LTD.

Mar 14 1994
(date)

cc: Dr. Thérèse M. Ast, U.S. Agent
Attorney-at-law
176 East 71st Street, New York, NY 10021
Via PUROLATOR COURIER (Waybill # 303 491 7959)

RECEIVED

MAR 15 1994

GENERIC DRUGS



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copy

novopharm

5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5
Telephone (416) 642-4550

file name 2/2/94

Fax #
(416) 642-4591

Mr. Douglas L. Sporn
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Metro Park North II (MPN II)
7500 Standish Place, Room 150
Rockville, MD
U.S.A. 20855-2773

NEW CORRESPONDENCE

ORIG NEW SERIES

Dear Mr. Sporn:

Subject: ANDA # 74-446
Terazosin Hydrochloride Tablets
1 mg, 2 mg, 5 mg, and 10 mg

This New Correspondence to our abbreviated new drug application for Terazosin Hydrochloride Tablets 1 mg, 2 mg, 5 mg, and 10 mg is in response to your letter dated February 3, 1994 that we received on February 11, 1994, from Mr. Robert W. Pollock, Director of Division of Labeling and Program Support.

Enclosed is a copy of our certification that the Field Copy is a true copy of the technical section of the application. Please note that this statement was included with the original Field Copy of the application submitted December 22, 1993. In future, this certification will be part of the cover letter of our applications.

If there are any questions with respect to this correspondence, you may direct written and telephoned communications to Thérèse Ast at (212) 439-6400 or (212) 439-9252, or you may contact Novopharm directly at 1-800-361-3313.

Yours sincerely,

Vivienne Richards

Vivienne Richards, B.Sc., M.A.
Director U.S. Regulatory Affairs
NOVOPHARM LTD.

Feb 14 1994

(date)

cc: Dr. Thérèse M. Ast, U.S. Agent
Attorney-at-law
176 East 71st Street, New York, NY 10021

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FEB 16 1994

GENERIC DRUGS

Via PUROLATOR COURIER (Waybill #286 913 9051)



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novopharm

Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5

Telephone (905) 642-4550
Fax (905) 642-4591

January 7, 1994

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

**ANDA
CORRESPONDENCE**

NEW CORRESP
Nc

Dear Ms Parise:

Subject: **ANDA Filed Dec. 22, 1993**
Terazosin Hydrochloride Tablets, 1 mg, 2 mg, 5 mg and 10 mg

This correspondence is in response to your telephone communication on January 7, 1994 to our agent, Dr. Therese Ast, concerning the exclusivity statement for this ANDA.

We have revised the exclusivity statement to certify that we will not claim for the indication of symptomatic benign prostatic hyperplasia until its exclusivity period has expired. A copy of the revised statement is included.

Please feel free to contact us directly at 1-800-361-3313 or our U.S. agent, Dr. Therese Ast, at (212) 439-9252 or (212) 439-6400.

Yours sincerely,

Vivienne Richards, B.Sc., M.A.
Director, U.S. Regulatory Affairs
NOVOPHARM LTD.

cc: Dr. Therese M. Ast,
176 East 71st Street, New York, NY 10021

Via PUROLATOR COURIER (Waybill # 303 491 7165)

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JAN 11 1994

GENERIC DRUGS

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novopharm

Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5

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11/6/93*

Telephone (905) 642-4550
Fax (905) 642-4591

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

Dear Mr. Sporn:

RE: **Abbreviated New Drug Application**
TERAZOSIN HYDROCHLORIDE TABLETS
1 MG, 2 MG, 5 MG, AND 10 MG

We are pleased at this time to make an original Abbreviated New Drug Application for our product - Terazosin Hydrochloride Tablets (1 mg, 2 mg, 5 mg, and 10 mg).

The purpose of this application is to gain FDA approval to market Terazosin Hydrochloride Tablets (1 mg, 2 mg, 5 mg, and 10 mg) in the U.S.A. The drug product described above is the same as HYTRIN[®], manufactured by Abbott Laboratories. We have submitted comparative information to indicate that our product is the same as the listed drug. This information is presented in tabular form, comparing active ingredient, conditions of use, route of administration, dosage form, strength, bioequivalence, and labeling for the products as supplied by Novopharm Ltd. and by Abbott Laboratories.

We have enclosed one (1) archival, one (1) review, and one (1) field copy of the application in accordance with 21 CFR § 314.55. As required, three (3) additional separately bound copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient and finished dosage form) are included as one of the volumes of the archival copy of this ANDA. The number of volumes in the archival, review, and field copies of the ANDA are as follows:

Blue Archival Copy - 6 volumes
Orange Review Copy - 3 volumes
Red Review Copy - 4 volumes
Burgundy Field Copy - 3 volumes

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DEC 23 1993

GENERIC DRUGS

Cont'd .../2

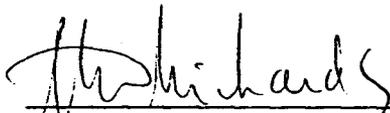


Mr. Douglas L. Sporn
re. Terazosin Hydrochloride Tablets
1 mg, 2 mg, 5 mg, and 10 mg
Page 2 of 2

In addition, we have also enclosed a computer diskette with the analytical data and bioavailability parameters in the format prescribed by the FDA. This diskette is located at the front of Section VI of the Orange Review Copy of this application.

We trust the information submitted is sufficient for this abbreviated new drug application to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Thérèse Ast at (212) 439-6400 or (212) 439-9252, or you may contact Novopharm directly at 1-800-361-3313. A letter of authorization, allowing Thérèse M. Ast to act as our U.S. agent, is in Section XXI.2.b of this application.

Yours sincerely,



Vivienne Richards, B.Sc., M.A.
Director, U.S. Regulatory Affairs
NOVOPHARM LTD.

December 16, 1993
(date)

cc: Dr. Thérèse M. Ast, Ph. D., Esq.
U.S. Agent
176 East 71st Street, New York, NY 10021

Via PUROLATOR COURIER (Waybill #286 913 9010)