# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**74-971**

## CORRESPONDENCE

novopharm
Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

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

***Telephone Amendment***

RE: **ANDA # 74-971**
**Ketoconazole Tablets, 200 mg**

We are filing this Telephone Amendment in response to the September 18, 1998 telephone call from Mr. Joe Buccine with respect to our ANDA for Ketoconazole Tablets, 200 mg. In this call, Mr. Buccine requested that we submit dissolution data which responds to the bioequivalency comments from the bioequivalence letter dated September 14, 1998.

We are including one (1) archival, one (1) review and one (1) field copy of this amendment in accordance with 21 CFR §314.94. 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, please feel free to contact us directly by telephone at 1-800-361-3313 or by fax at (905)-642-4590.

Yours sincerely,

SEP 2 3 1998

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

(date)

cc. Dietrich Bartel, B.Sc.
Director, Regulatory Affairs
Novopharm N.C. Inc.
4700 Novopharm Blvd.
Wilson, NC
U.S.A. 27893

Via FEDEX (Waybill no. 400-0741-3766)

RECEIVED
SEP 24 1998
GENERIC DRUGS

MEMBER CDMA

novopharm
Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

Do noted. NAF 4/30/99

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
USA 20855-2773

***MINOR AMENDMENT***

**Subject:** **ANDA # 74-971**
**Ketoconazole Tablets USP, 200 mg**

Pursuant to your letter of October 14, 1998 (tentative approval for Ketoconazole Tablets USP, 200 mg), we are advising you that there are no further changes in the conditions under which the products were tentatively approved.

In addition, as per the Guidance for Industry - Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 (Revised July 1998), the "Rx Only" statement will replace the "Caution: Federal law prohibits dispensing without prescription" statement. Please note that no other changes will be made in our labeling and will be submitted in the next annual report, since our original ANDA was received by the Agency prior to February 19, 1998.

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 application and has been submitted to the Office of Generic Drugs.

If there are any questions with respect to this submission, please do not hesitate to contact Novopharm directly by telephone at 1-800-361-3313 or by fax at 1-905-642-4590.

Yours sincerely,

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

MAR 15 1999
(date)

RECEIVED
MAR 16 1999
GENERIC DRUGS

3/19/99

MEMBER COMA

aring

— 41 **novopharm**

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

Telephone (905) 642-4550
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 20855-2773

*TELEPHONE AMENDMENT*

NDA ORIG AMENDMENT
N/A M1

RE: **ANDA # 74-971**
**KETOCONAZOLE TABLETS USP, 200 MG**

We are filing this **Telephone Amendment** in response to the September 14, 1998 call from Mr. Joe Buccine, FDA. In this call, Mr. Buccine requested that we confirm that the method of dissolution testing for stability and quality control is in accordance with that requested by the Division of Bioequivalence.

Dissolution testing for finished product release and shelf life stability is conducted using house method K-015-02 Version 1.20S, which specifies the use of 900 mL of 0.1N HCl at 37°C using USP 23 Apparatus II (paddle) at 50 rpm. The specification for the test product is: NLT of the labeled amount of the drug in the dosage form dissolved in 30 minutes. This methodology was submitted to FDA on May 16, 1997, in response to the March 5, 1997 request from the Division of Bioequivalence.

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

If there are any questions or comments with respect to this Amendment, please direct written communications to Novopharm N.C. Inc. by fax at (919) 234-2600 (phone: (919) 234-2222 or (919) 234-2212). Telephone communications can be directed to Novopharm Limited at 1-800-361-3313 or (905) 642-4550 (fax: (905) 642-4590).

Yours sincerely,

SEP 15 1998

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

(date)

RECEIVED
SEP 16 1998
GENERIC DRUGS

cc: Dietrich Bartel, Director, Regulatory Affairs, Novopharm N.C. Inc.,
4700 Novopharm Blvd., Wilson, N.C., U.S.A. 27893

MEMBER CDMA

BIOEQUIVALENCY COMMENTS

ANDA: 74-971 APPLICANT: Novopharm Ltd.

DRUG PRODUCT: Ketoconazole Tablets, 200 mg

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

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

> The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP23 Apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

novopharm
Novopharm Limited
5691 Main Street West, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
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 20855-2773

*TELEPHONE AMENDMENT*

NDA ORIG AMENDMENT
N/ Am1

RE: **ANDA # 74-971**
**KETOCONAZOLE TABLETS USP, 200 MG**

We are filing this Amendment in response to the August 13, 1998 telephone conversation between Mr. Joe Buccine, FDA, and Mr. Dietrich Bartel, Director, Regulatory Affairs, Novopharm N.C. Inc. In this call, Mr. Buccine requested that we revise the specification for total impurities for ketoconazole raw material, submitted in our July 21, 1998 Minor Amendment, from Updated specifications for the drug substance, incorporating the new limit, are included in the following pages.

Also, pursuant to 21 CFR § 314.50 (a) (5), we hereby inform you that effective August 3, 1998, Novopharm Limited has changed its U.S. Agent. Our new authorized responsible official's name, address and contact number are:

Dietrich Bartel, B.Sc.
Director, Regulatory Affairs
Novopharm N.C. Inc.
4700 Novopharm Blvd.
Wilson, NC
U.S.A. 27893

Telephone: (919) 234-2222 or (919) 234-2212
Fax: (919) 234-2600

We have attached a letter of authorization allowing Dietrich Bartel to act as our authorized U.S. responsible official in the following pages.

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

RECEIVED
SEP 0 1 1998
GENERIC DRUGS

.../2

*Telephone Amendment*
*ANDA # 74-971*
*Ketoconazole Tablets USP, 200 mg*

If there are any questions or comments with respect to this Amendment, please direct written communications to Novopharm N.C. Inc. by fax at (919) 234-2600 (phone: (919) 234-2222 or (919) 234-2212). Telephone communications can be directed to Novopharm Limited at 1-800-361-3313 or by fax at (905) 642-4590.

Yours sincerely,

AUG 3 1 1998

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

(date)

cc:

7-22-98
4.1

**novopharm**

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

Telephone (905) 642-4550
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 20855-2773

***MINOR AMENDMENT***

ORIG
N/A

RE: **ANDA # 74-971**
**KETOCONAZOLE TABLETS USP, 200 MG**

We thank you for your letter dated April 29, 1998, which we received on April 30, 1998, from Dr. Rashmikant M. Patel, Division of Chemistry I. This letter was in response to our ANDA and Amendments for Ketoconazole Tablets USP, 200 mg.

For ease of review, Dr. Patel's comments have been restated in **bold** print, followed by our response.

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

Should you have any further comments or questions, please do not hesitate to contact us directly by phone at 1-800-361-3313 or by fax at 1-905-642-4590.

Yours sincerely,

RECEIVED JUL 2 1 1998

(date)

JUL 2 2 1998

GENERIC DRUGS

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

cc: Dr. Thérèse M. Ast, Ph. D., Esq., U.S. Agent, Novopharm N.C. Inc., 4700 Novopharm Blvd., Wilson, N.C. 27893

7-23-98

MEMBER CDMA

BIOEQUIVALENCY COMMENTS

ANDA: 74-971 APPLICANT: Novopharm Ltd.

DRUG PRODUCT: Ketoconazole Tablets, 200 mg

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

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

> The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP23 Apparatus II(paddle) at 50 rpm. The test product should meet the following specifications:

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

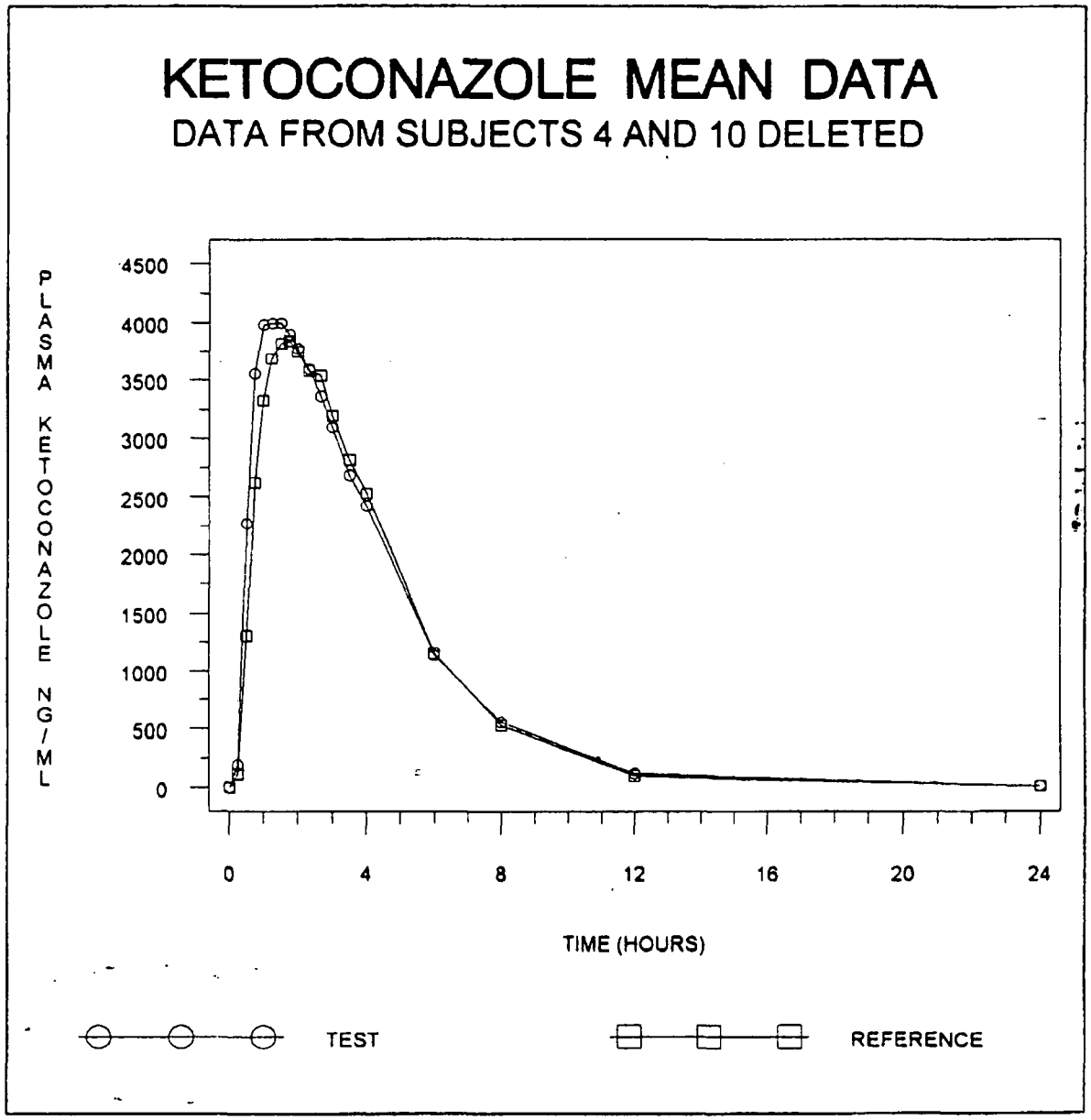
/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

WP# 7497/S.798 Attachment (1 of 1)



Figure 4.5.3 Linear Plot of Mean Plasma Ketoconazole Concentrations *vs* Time




1016

novopharm
Novopharm Limited
5691 Main Street, Stouffville, Ontario, Canada L4A 1H5
Telephone (905) 642-4550
Fax (905) 642-4591

FPL
MAJOR AMENDMENT
AC

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 20855-2773

*MAJOR AMENDMENT*

RECEIVED
NOV 13 1997
GENERIC DRUGS

RE: **ANDA # 74-971**
**KETOCONAZOLE TABLETS USP, 200 MG**

We thank you for your letters dated April 25, 1997, which we received on April 28, 1997, from Dr. Rashmikant M. Patel, Division of Chemistry I, and Mr. Jerry Phillips, Division of Labeling and Program Support. These letters were in response to our ANDA submitted on September 30, 1996 for Ketoconazole Tablets USP, 200 mg.

For ease of review, Dr. Patel's and Mr. Phillip's comments have been restated in **bold** print, followed by our response.

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

Should you have any further comments or questions, please do not hesitate to contact us directly by phone at 1-800-361-3313 or by fax at 1-905-642-4590.

Yours sincerely,

NOV 12 1997

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

(date)

cc: Dr. Thérèse M. Ast, Ph. D., Esq., U.S. Agent, Novopharm N.C. Inc., 4700 Novopharm Blvd., Wilson, N.C. 27893

VIA FEDERAL EXPRESS

Table of Contents
Response to Chemistry Deficiencies
Response to Comment # 1
Response to Comment # 2

ANDA 74-971

OCT - 7 1997

Novopharm NC, Inc.
Attention: Thérèse Ast
Authorized U.S.Agent for Novopharm
4700 Novopharm Drive
Wilson, NC 27893

Dear Madam:

Reference is made to the Abbreviated New Drug Application, and the amendment submitted on May 16, 1997, for Ketoconazole Tablets USP, 200 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. In addition to the possibility of "product failure", there is also the possibility of the existence of a "subpopulation", for which low plasma levels of the drug may be observed.

   According to the Guidances *Statistical Procedures for Bioequivalence Studies* (issued by the Division of Bioequivalence July 1, 1992), *"The existence of an outlier could be indicative of the following problems with interchangeability of two formulations:*

   a. *Product failure: a subject obtained an unusually high or low response to one or the other of the products because of a problem with the specific dosage unit(s) administered. Examples include a sustained/modified release dosage form exhibiting dose dumping or a dosage unit whose coating inhibited dissolution.*

   b. *Subpopulation: a subject may be representative of a type of subject, present in the general population in low numbers, for whom the relative bioavailability of the two products is markedly different than it is for the majority of the population, and for whom the two products are not bioequivalent, even though they might be bioequivalent in the majority of the population.*

*In the case of product failure, it could make a difference whether the unusual response is observed on the test product or the reference product. In the case of a subpopulation, however,* ***even if the unusual response is observed on the reference product,*** *there could still be concern for lack of interchangeability of the two products."*

Since the existence of a "subpopulation" can not be ruled out based on the data on hand, the exclusion of the "outlier" subjects from the statistical analysis is not completely justified.

2. You may consider, if possible, **redosing the same "outlier" subjects** to confirm or to eliminate the possibility of a "subpopulation". These subjects should be redosed with other "control" subjects, who also participated in the study previously and were without the unusual plasma levels of the drug. If the same "outlier" subjects no longer exhibit the unusually low plasma levels, then the possibility of "product failure" may be confirmed, and the exclusion of data from these subjects may become acceptable.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

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

ANDA 74-971

MAR - 5 1997

Novopharm, LTD.
Attention: Dietrich Bartel
5691 Main Street West
Stouffville, Ontario
CANADA L4A 1H5

Dear Sir:

Reference is made to the bioequivalence data submitted on September 30, and December 5, 1996 for Ketoconazole Tablets USP, 200 mg.

The Office of Generic Drugs has reviewed the submitted bioequivalence data and the following comments are provided for your consideration:

1. The single-dose, fasting bioequivalence study (Protocol No. 1552-1) conducted by Novopharm Ltd. on its test product, Ketoconazole Tablets, 200 mg, lot # 3040PD, comparing it with the reference product, Nizoral[R] Tablets, 200 mg, lot # 94E303A, (Janssen) is **not acceptable.** The 90% confidence intervals for log-transformed $AUC_{(0-T)}$, $AUC_{(0-Inf)}$ and $C_{MAX}$ are outside the acceptable limit of [0.80;1.25].

   According to the Guidance *Statistical Procedures for Bioequivalence Studies* (issued by the Division of Bioequivalence July 1, 1992), data from Subjects 4 and 10 should not be excluded from the data analyses "solely on the basis of a statistical test", "scientific evidence or explanations to justify the exclusion of the subjects data from statistical analysis" are required. As indicated in the final report, there were no noted clinical anomalies with any of these subjects, and the chromatography was consistent for both dosing periods for each subject.

2. The single-dose, non-fasting bioequivalence study conducted by Novopharm Ltd. on its test product, Ketoconazole Tablets, 200 mg, lot # 3040PD, comparing it with the reference product, Nizoral[R] Tablets, 200 mg, lot # 94E303A, has been found **incomplete.** The long-term stability study for the non-fasting study fails to demonstrate that the plasma samples were stable for the entire sample storage duration of 69 days. The long-term stability study covered only a 64-day period.

3. The *in vitro* dissolution testing conducted by Novopharm Ltd. on its Ketoconazole Tablets, 200 mg, has been found incomplete; the dissolution specification should include the actual sampling time of the dissolution testing (e.g., 30 minutes, 40 minutes or 50 minutes ...). We recommend, based on the dissolution data submitted, that the tentative specification should be [redacted].

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment must address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

for Nicholas Fleischer, Ph.D.
Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research