Ketamine Hydrochloride
Injectable USP, 50 mg/mL
filled in 10 mL vials
ANDA #76-092
Reviewer: Andre Jackson
V:\Firmsam\Bioniche\Ltr&Rev\76092W.301

Bioniche Pharma
U.S. Agent-Robert Pitts
Athens, Georgia
Submission Date:
March 8, 2001

Review of a Waiver Request

History:

The original submission on December 21. 2000 was for three strengths [redacted], 50 mg/mL and [redacted]. The Office of Generic Drugs responded to this submission with a refuse to file for the [redacted] and [redacted] strengths (see FDA letter February 16, 2001). The firm subsequently withdrew the [redacted] and [redacted] strengths.

Introduction:

Ketamine Hydrochloride is a rapid-acting nonbarbiturate general anesthetic. The drug product is a solution intended solely for intravenous and intramuscular administration.

The firm has requested a waiver of *in vivo* bioequivalence study requirements for its drug product, Ketamine Hydrochloride Injection, USP, 50 mg/mL, in 10 mL vials.

Table 1. Formulation Comparison

	Test	**Reference**
	Ketamine HCl	Ketalar®
	(mg/mL)	(mg/mL)
Ketamine, USP (Hydrochloride)	50.0	50.0
Benzethonium Chloride	0.1	0.1

Comments

1.The composition of the test (Ketamine Hydrochloride Injection, USP, 50 mg/mL, filled in 10 mL vials) and reference(Ketalar^R, 50 mg/mL, filled in 10 mL vials) products are presented in Table 1. Both test and reference products contain the same amount of active and inactive drug ingredients.

2.The route of administration, dosage form, and strength of the proposed Bioniche Pharma's products are identical with that of the reference listed drug Ketalar^R marketed by Parke-Davis.

Recommendation:

1.The Division of Bioequivalence agrees that the information submitted by Bioniche Pharma demonstrates that Ketamine Hydrochloride Injection, USP, 50 mg/mL, filled in 10 mL vials, and the reference product, Ketalar^R, 50 mg/mL, filled in 10 mL vials falls under 21 CFR Section 320.22 (b)(1)of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for , 50 mg/mL, filled in 10 mL vials of the test product is granted. Therefore, from the bioequivalence point of view, the Division of Bioequivalence deems Ketamine Hydrochloride Injection, USP, 50 mg/mL, filled in 10 mL vials manufactured by Bioniche Pharma to be bioequivalent to the reference products, Ketalar^R , 50 mg/mL, and filled in 10 mL vials manufactured by Parke-Davis.

Andre Jackson, Ph. D.
Division of Bioequiva...
Review Branch I

/S/

RD INITIALED YC HUANG
FT INITIALED YC HUANG

/S/ Date: 4/26/2001

Concur: /S/ Date: 4/30/2001
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

fw

cc:ANDA # 76-092 (original, duplicate), HFD-652 (Jackson, Huang), HFD-650(Director), Drug File, Division File

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-092

ADMINISTRATIVE DOCUMENT(S)

Record of Telephone Conversation

The firm originally withdrew the [redacted] strength. Then submitted a suitability petition for the [redacted] and recently added the [redacted] to the application again. We were ready to approve the application for the 50 mg but became aware of the addition of the [redacted] The application only has FPL for the 50 mg and Bioequivalence was only approved for the 50 mg. The [redacted] strength was not reviewed for Bioequivalence, Chemistry, or Labeling. The firm had 3 options:

1) Withdraw the [redacted] and submit it as a new ANDA.

2) Withdraw the [redacted] wait for the application to get approved then submit a new strength supplement.

3) Or we can review the [redacted] but the that means Bioequivalence, Chemistry, and Labeling will be reviewed as a Major. Also you will need to submit FPL for the 50 mg and [redacted]

Rhonda Knoll stated the she will withdraw the [redacted] strength and submit it as a new ANDA application.

Date:
November 14, 2001

ANDA Number:
76-092

Product Name:
Ketamine

Firm Name:
Bioniche

Firm Representative:
Rhonda Noll

Phone Number:
1-800-567-2028

FDA Representative:
Jeen Min
Glen Smith

Signatures:
/S/ 11/19/01

CC: ANDA 76-092

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-092

CORRESPONDENCE

BIONICHE
PHARMA GROUP
A BIONICHE LIFE SCIENCES COMPANY

NEW CORRESP

November 20, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Telephone Amendment
ANDA 76-092

Attention: Jeen Min, Project Manager

RE: **ANDA 76-092**
KETAMINE HYDROCHLORIDE INJECTION, USP 50 MG/ML (BASE)

Further to your telephone call this afternoon, November 20, 2001, please find attached all of the missing 356h forms. Sorry for any inconvenience this may have caused you.

If you have any questions please feel free to contact me directly at 1-800-567-2028.

Yours sincerely,

Rhonda Noll
Regulatory Affairs Manager
Bioniche Pharma (Canada) Ltd.

NOV 2 1 2001
EVALUATION AND RESEARCH

Attached

BIONICHE PHARMA (CANADA) LTD • BIONICHE PHARMA GROUP LIMITED • BIONICHE TEORANTA
151 DUNDAS STREET, SUITE 507, LONDON, ON N6A 5R7 • TEL: (519) 453 0641 • FAX: (519) 453 6169
BIONICHE TEO • INVERIN, CO. GALWAY, REPUBLIC OF IRELAND • PHONE: 353-91-593202 • FAX: 353-91-593228
WEBSITE: WWW.BIONICHE.COM

BIONICHE
PHARMA GROUP
A BIONICHE LIFE SCIENCES COMPANY

November 14, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Withdrawal Letter
ANDA 76-092

[redacted] CORRESP
NC

Attention: Jeen Min, Project Manager

RE: **ANDA 76-092**
KETAMINE HYDROCHLORIDE INJECTION, USP [redacted]

Further to our conference call this morning, November 14, 2001, please note that Bioniche Pharma (Canada) Ltd, at this time, would like to withdraw, under [21 CFR 314.99], the reinstatement request for the [redacted] vial, dated September 5, 2001, in order to allow the review of the Ketamine HCl Injection, USP 50 mg/mL to continue. (Letter attached)

We will submit a new ANDA for the Ketamine HCl USP, [redacted] based on the approved suitability petition, at a later date.

If you have any questions please feel free to contact me directly at 1-800-567-2028.

Yours sincerely,

Rhonda Noll

Rhonda Noll
Regulatory Affairs Manager
Bioniche Pharma (Canada) Ltd.

CENTER FOR DRUG EVALUATION AND RESEARCH
NOV 2 0 2001
[redacted]

Attached

BIONICHE PHARMA (CANADA) LTD • BIONICHE PHARMA GROUP LIMITED • BIONICHE TEORANTA
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WEBSITE: WWW.BIONICHE.COM

BIONICHE
PHARMA GROUP
A BIONICHE LIFE SCIENCES COMPANY

November 6, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Microbiology Amendment
ANDA 76-092

ORIG AMENDMENT

Attention: Jeen Min, Project Manager

RE: **ANDA 76-092**
KETAMINE HYDROCHLORIDE INJECTION, USP 50 MG/ML (BASE)

Further to the Microbiology Deficiencies fax, dated October 24, 2001, please find attached Bioniche Pharma (Canada) Ltd's response in comment and response format.

If you have any questions please feel free to contact me directly at 1-800-567-2028.

Yours sincerely,

Rhonda Noll
Regulatory Affairs Manager
Bioniche Pharma (Canada) Ltd.

RECEIVED FOR DRUG EVALUATION AND RESEARCH
NOV 07 2001
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Attached

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WEBSITE: WWW.BIONICHE.COM

1 Cm/M

BIONICHE
PHARMA GROUP
A BIONICHE LIFE SCIENCES COMPANY

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ORIG AMENDMENT
DERT LOL

September 25, 2001

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

Minor Amendment
ANDA 76-092

Attention: Jeen Min, Project Manager

RE: **ANDA 76-092**
KETAMINE HYDROCHLORIDE INJECTION, USP 50 MG/ML (BASE)

Further to the Minor Amendment fax, dated August 23, 2001, please find attached Bioniche Pharma (Canada) Ltd's response in comment and response format.

If you have any questions please feel free to contact me directly at 1-800-567-2028.

Yours sincerely,

(Fax) 519-453-2418.

Rhonda Noll

Rhonda Noll
Regulatory Affairs Manager
Bioniche Pharma (Canada) Ltd.

CENTER FOR DRUG EVALUATION AND RESEARCH
SEP 26 2001

Attached

/S/
9/24/01

1 copy

BIONICHE
PHARMA GROUP
A BIONICHE LIFE SCIENCES COMPANY

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

Amendment to ANDA 76-092

ORIG AMENDMENT
AA

Attention: Mr. Peter Rickman

RE: **ANDA 76-092**
KETAMINE HYDROCHLORIDE INJECTION, USP 50 MG/ML (BASE)

Pursuant to section 314.96 of 21 CFR, Bioniche Pharma (Canada) Ltd. would like to, at this time, amend our Ketamine Hydrochloride Injection, USP 50 mg/mL (base), ANDA 76-092.

In our recent FDA Audit, April 30 to May 5, it was noted that our current manufacturing order for the above product does not reflect the correct [redacted] The manufacturing order states a cycle of [redacted] when in fact we actually [redacted]. Therefore we have amended our Manufacturing Order to reflect the correct cycle.

If you have any questions please feel free to contact me directly at 1-800-567-2028.

Yours sincerely,

Rhonda Noll

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 24 2001
OGD

May 23/01
(date)

Rhonda Noll
Regulatory Affairs Manager
Bioniche Pharma (Canada) Ltd.

Attached

BIONICHE
PHARMA GROUP
A BIONICHE LIFE SCIENCES COMPANY

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

Amendment to ANDA 76-092

NEW CORRESP
NC

Attention: Mr. Peter Rickman

RE: **ANDA 76-092**
KETAMINE HYDROCHLORIDE INJECTION, USP 50 MG/ML (BASE)

Pursuant to section 314.96 of 21 CFR, Bioniche Pharma (Canada) Ltd. would like to, at this time, amend our Ketamine Hydrochloride Injection, USP 50 mg/mL (base), ANDA 76-092.

Following withdrawal of the [redacted] and [redacted] strengths from the original ANDA for the above product (see correspondence dated December 21, 2000 and March 8, 2001), we have reviewed the data which supports validation of the [redacted]. The data in the ANDA indicates that the [redacted] vial of Ketamine Hydrochloride Injection is valid. We are planning to complete additional terminal sterilization validation on the 50 mg/mL, 10 mL package, in order to provide supportive information for the submission. At that time we will also complete [redacted] validation studies for the 50 mg/mL strength, as the data in the submission supports the [redacted] strength.

It is our intention to submit the additional validation information by September 2001. We will also be placing the validation batches on stability and will amend our stability section at that time as well.

If you have any questions please feel free to contact me directly at 1-800-567-2028.

Yours sincerely,

Rhonda Noll

Rhonda Noll
Regulatory Affairs Manager
Bioniche Pharma (Canada) Ltd.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
APR 06 2001
OGD

April 5/01
(date)

Cc: Bob Pitts

BIONICHE PHARMA (CANADA) LTD • BIONICHE PHARMA GROUP LIMITED • BIONICHE TEORANTA
151 DUNDAS STREET, SUITE 507, LONDON, ON N6A 5R7 • TEL: (519) 453 0641 • FAX: (519) 453 6169
BIONICHE TEO • INVERIN, CO. GALWAY, REPUBLIC OF IRELAND • PHONE: 353-91-593202 • FAX: 353-91-593228
WEBSITE: WWW.BIONICHE.COM

ANDA 76-092

MAR 13 2001

Vetrepharm Research Inc.
U.S. Agent for Bioniche Pharma
Attention: Robert Pitts
119 Rowe Road
Athens, GA 30601

Dear Sir:

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

Reference is made to our "Refuse to Receive" letter dated February 16, 2001 and your amendment dated March 8, 2001.

In addition, we acknowledge the receipt of your communication dated March 12, 2001, requesting withdrawal of the [redacted] and the [redacted] 10 ml vials from your abbreviated new drug application for Ketamine Hydrochloride Injection USP, [redacted] 50 mg(base)/mL, 10 mL vials and [redacted] vials.

In compliance with your request and in accordance with Section 314.65 of the regulations under the Federal Food, Drug and Cosmetic Act, the [redacted] and [redacted] vials from your application are regarded as withdrawn. This withdrawal does not prejudice any future filing of the application. You may request that the information in this application be considered in connection with any resubmission.

NAME OF DRUG: Ketamine Hydrochloride Injection USP, 50 mg(base)/mL, 10 mL vials

DATE OF APPLICATION: December 21, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 12, 2001

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

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

Should you have questions concerning this application, contact:

Jeen Min
Project Manager
(301) 827-5849

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BIONICHE
PHARMA GROUP
A BIONICHE LIFE SCIENCES COMPANY

N/AC

ORIG AMENDMENT

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

Refusal to Receive
ANDA 76-092

505(j)(2)(A)(i) OK
/S/ 3-MAR-2001
/S/

Attention: Mr. Peter Rickman

RE: **ANDA 76-092**
KETAMINE HYDROCHLORIDE INJECTION, USP
10 MG/ML, 50 MG/ML AND

In response to your letter dated February 16, 2001, please find enclosed, following this letter, the revised 356h form and the signed certificates of current Good Manufacturing Practices for the two contract firms utilized in the submission,

Please note that at this time we would like to withdraw, under [21 CFR 314.99], the and the , in order to allow for the 50 mg (base)/mL, 10 mL vial ANDA review to proceed.

Bioniche Pharma plans to submit an ANDA suitability petition, under [21 CFR 314.93], to gain approval for the vial. Once approval is received we would like to reinstate the vial for review.

If you have any questions please feel free to contact me directly at 1-800-567-2028.

Yours sincerely,

Rhonda Noll

Rhonda Noll
Regulatory Affairs Manager
Bioniche Pharma (Canada) Ltd.

March 8/01
(date)

Cc: Bob Pitts

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 12 2001
OGD

BIONICHE PHARMA (CANADA) LTD • BIONICHE PHARMA GROUP LIMITED • BIONICHE [illegible]
151 DUNDAS STREET, SUITE 507, LONDON, ON N6A 5R7 • TEL: (519) 453 0641 • FAX: (519) [illegible]
BIONICHE TEO • INVERIN, CO. GALWAY, REPUBLIC OF IRELAND • PHONE: 353-91-593202 • FAX: 353-91-593228
WEBSITE: WWW.BIONICHE.COM

ANDA 76-092

Vetrepharm Research Inc.
U.S. Agent for Bioniche Pharma
Attention: Bob Pitts
119 Rowe Road
Athens, GA 30601

FEB 16 2001

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated December 21, 2000, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Ketamine Hydrochloride Injection USP, [redacted] 50 mg(base)/mL, 10 mL vials and [redacted] vials.

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

We are refusing to receive this application under 21 CFR 314.101(d)(3) for the following reasons:

Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug (RLD). An applicant may only seek approval of a parenteral product if it differs from the RLD in preservative, buffer, or antioxidant [21 CFR 314.94(9)(iii)]. Your formulation for your [redacted] which is not an allowable change for a parenteral product.

Your proposed formulation for the [redacted] does not meet the bioequivalence waiver requirements under 21 CFR 320.22(b)(1). To be eligible for a waiver of evidence of in vivo bioequivalence under 21 CFR 320.22(b)(1), your proposed product must contain the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application. Ketamine Hydrochloride Injection USP, [redacted], does not contain the same inactive ingredients as the reference listed product.

Any applicant who wishes to submit an abbreviated new drug application for a drug product which is not identical to the RLD in strength must first obtain permission from the agency

to submit such an abbreviated application. A change in the total drug content is considered a change in strength. The RLD does not contain a [redacted] vial size. Therefore, you are required to have an approved ANDA suitability petition for a change in strength from the RLD before you can submit an ANDA for this strength [21 CFR 314.93].

Please revise your 356h form to state the correct number of volumes and have the form originally signed by your authorized U.S. Agent.

The application lacks a certification of compliance with Current Good Manufacturing Practices (CGMP) and/or Good Laboratory Practice (GLP) by all the outside firms utilized in this application. Please submit CGMP/GLP Certification for [redacted] and [redacted]

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

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Emily Thomas
Project Manager
(301) 827-5862

Sincerely yours,

/S/

Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

We trust the information submitted is sufficient for this Abbreviated New Drug Application to be evaluated. If there are any questions or comments with respect to this application, please direct written communications to **Mr. Bob Pitts** by **fax at (1-706-548-0659:)**. Telephone communications can be directed to Bioniche Pharma (Canada) Ltd.. at 1-800-567-2028 or by fax at (519) 453-0641.

A letter of authorization, allowing **Mr. Bob Pitts**, to act as our responsible official in the U.S.A. is included in Section XX. 2 of this application.

I would like to bring to your attention that throughout this submission some of the submitted material will mention the company name Vetrepharm Research Inc. Vetrepharm Research Inc. and Bioniche Pharma (Canada) Ltd. are both connected under the same parent company Bioniche Life Sciences.

Yours sincerely,

Rhonda Noll

December 21/00
(date)

Rhonda Noll
Regulatory Affairs Manager
Bioniche Pharma (Canada) Ltd.

cc. Bob Pitts