

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 \_\_\_\_\_, 50 mg/mL and \_\_\_\_\_. The Office of Generic Drugs responded to this submission with a refuse to file for the \_\_\_\_\_ and \_\_\_\_\_ strengths (see FDA letter February 16, 2001). The firm subsequently withdrew the \_\_\_\_\_ and \_\_\_\_\_ 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

	<u>Test</u>	<u>Reference</u>
	Ketamine HCl	Ketalar <sup>R</sup>
	(mg/mL)	(mg/mL)
Ketamine, USP	50.0	50.0
(Hydrochloride)		
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<sup>R</sup>, 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<sup>R</sup> 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<sup>R</sup>, 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<sup>R</sup> , 50 mg/mL, and filled in 10 mL vials manufactured by Parke-Davis.

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

*[Signature]*

RD INITIALED YC HUANG  
FT INITIALED YC HUANG

*[Signature]*

*[Signature]*

Date: 4/26/2001

Concur: Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence

*fw*

*[Signature]*

Date: 4/30/2001

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

<p>The firm originally withdrew the _____ strength. Then submitted a suitability petition for the _____ and recently added the _____ to the application again. We were ready to approve the application for the 50 mg but became aware of the addition of the _____. The application only has FPL for the 50 mg and Bioequivalence was only approved for the 50 mg. The _____ strength was not reviewed for Bioequivalence, Chemistry, or Labeling. The firm had 3 options:</p> <ol style="list-style-type: none"><li>1) Withdraw the _____ and submit it as a new ANDA.</li><li>2) Withdraw the _____ wait for the application to get approved then submit a new strength supplement.</li><li>3) Or we can review the _____, 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 _____.</li></ol> <p>Rhonda Knoll stated the she will withdraw the _____ strength and submit it as a new ANDA application.</p>	<p><b>Date:</b> November 14, 2001</p>
	<p><b>ANDA Number:</b> 76-092</p>
	<p><b>Product Name:</b> Ketamine</p>
	<p><b>Firm Name:</b> Bioniche</p>
	<p><b>Firm Representative:</b> Rhonda Noll</p>
	<p><b>Phone Number:</b> 1-800-567-2028</p>
	<p><b>FDA Representative:</b> Jeen Min Glen Smith</p>
<p><b>Signatures:</b> <i>JS/ 11/19/01</i></p>	

CC: ANDA 76-092

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**CENTER FOR DRUG  
EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**76-092**

**CORRESPONDENCE**



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.



Attached

**BIONICHE**  
P H A R M A G R O U P  
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*

~~CONFIDENTIAL~~  
NC

Attention: Jeen Min, Project Manager

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

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 \_\_\_\_\_ 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, \_\_\_\_\_ 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  
Regulatory Affairs Manager  
Bioniche Pharma (Canada) Ltd.



Attached



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*

Attention: Jeen Min, Project Manager

ORIG AMENDMENT

AS

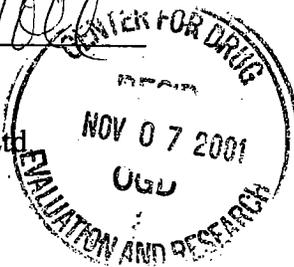
RE: **ANDA 76-092**  
**KETAMINE HYDROCHLORIDE INJECTION, USP 50 MG/ML (BASE)**

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



Attached

1 copy

N/AM  
ORIG AMENDMENT  
DEPT L&L

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

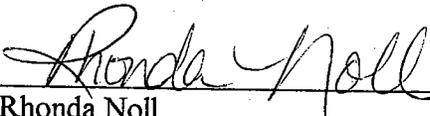
RE: **ANDA 76-092**  
**KETAMINE HYDROCHLORIDE INJECTION, USP 50 MG/ML (BASE)**

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  
Regulatory Affairs Manager  
Bioniche Pharma (Canada) Ltd.



Attached

151  
9/29/01



**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 \_\_\_\_\_ and \_\_\_\_\_ 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 \_\_\_\_\_. The data in the ANDA indicates that the \_\_\_\_\_ 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 \_\_\_\_\_ validation studies for the 50 mg/mL strength, as the data in the submission supports the \_\_\_\_\_ 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.



*April 5/01*  
(date)

Cc: Bob Pitts

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 ~~\_\_\_\_\_~~ and the ~~\_\_\_\_\_~~ 10 mL vials from your abbreviated new drug application for Ketamine Hydrochloride Injection USP, ~~\_\_\_\_\_~~ 50 mg(base)/mL, 10 mL vials and ~~\_\_\_\_\_~~ 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 ~~\_\_\_\_\_~~ and ~~\_\_\_\_\_~~ ~~\_\_\_\_\_~~ 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

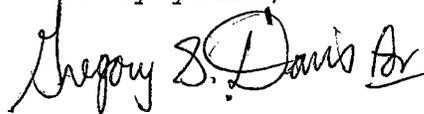
We will correspond with you further after we have had the opportunity to review the application.

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,

A handwritten signature in cursive script that reads "Gregory S. Davis" followed by a stylized flourish.

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

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

505022 (2)(A) OK  
3-MAR-2001  
/S/ /S/

Attention: Mr. Peter Rickman

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

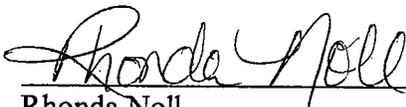
In response to your letter dated February 16, 2001, please find enclosed, following this letter, the revised 356h form and the signed certificates of current Good Manufacturing Practices for the two contract firms utilized in the submission,

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  
Regulatory Affairs Manager  
Bioniche Pharma (Canada) Ltd.

March 8/01  
(date)

Cc: Bob Pitts





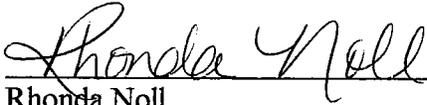


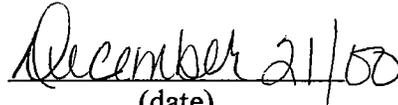
We trust the information submitted is sufficient for this Abbreviated New Drug Application to be evaluated. If there are any questions or comments with respect to this application, please direct written communications to **Mr. Bob Pitts** by **fax at (1-706-548-0659:)**. Telephone communications can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

  
(date)

cc. Bob Pitts