CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-092

CSO LABELING REVIEW(S)

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

ANDA Number: 76-092 Date of Submission: December 21, 2000 and March 8, 2001

Applicant's Name: Bioniche Pharma

Established Name: Ketamine Hydrochloride Injection USP, 50 mg (base)/mL

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. We acknowledge that you have withdrawn the ~~[redacted]~~ and ~~[redacted]~~ products.

   b. We ask that you include the symbol for the controlled substance III on all labels and labeling.

   c. We note that you identify the manufacturer of your drug product as "~~[redacted]~~. However, your description of manufacturing facility indicates that "Bioniche Teoranta, Inverin Co. Galway, Ireland" is the manufacturer. Please explain this discrepancy and/or revise.

2. CONTAINER – 10 mL

   a. See general comments above.

   b. We ask that you revise the expression of strength so that the total content appears as the primary expression of strength. We offer the following as ~~the~~ an example:

      500 mg /10 mL*
      (50 mg/mL)

   c. Include an asterisk in the "Each mL..." statement to read "*Each mL...".

   d. We encourage that you relocate the phrase **"For slow intravenous... use."** to the principal display panel, if space permits.

3. CARTON 10 x 10 mL

   a. See comments under CONTAINER.

   b. You drug product appears to be light sensitive. Please include the following statement in a prominent manner.

      Retain in carton until time of use.

4. INSERT

   a. GENERAL

      i. See general comments, where applicable.

ii. The following comments are based on the last approved labeling for Ketalar® (approved on February 14, 2001).

iii. Please note that USAN names are common nouns and should be treated as such in the text of labeling (*i.e.*, lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert.

iv. You may delete the term "USP" in association with the established name of your drug product throughout the text except in the DESCRIPTION, INDICATIONS AND USAGE, and HOW SUPPLIED sections.

v. It is preferable to use the term "mcg" rather than '— when referring to microgram.

b. TITLE

We encourage the inclusion of "Rx only" to appear beneath the title.

c. SPECIAL NOTE (Third paragraph, first sentence) – Revise to read:

...is least in the elderly (over 65 years of age) patient.

d. DESCRIPTION

i. Please delete reference to the _____, and _____ concentrations.

ii. We encourage the inclusion of the molecular weight. We refer you to 21 CFR 201.57(a).

e. PRECAUTIONS

i. General – Last paragraph, second sentence:

...with preanesthetic elevated cerebrospinal... [add "elevated"]

ii. Pediatric Use – Revise to read:

Safety and effectiveness in pediatric patients below the age of 16 have not been established.

f. DRUG ABUSE AND DEPENDENCE

...,but not limited to anxiety, dysphoria, disorientation, insomnia, flashbacks, hallucinations, and psychotic episodes. Ketamine dependence and tolerance are possible following prolonged administration. A withdrawal syndrome with psychotic features has been described following discontinuation of long-term ketamine use. Therefore...

g. DOSAGE AND ADMINISTRATION

i. First paragraph:

...*should not* be injected from the same syringe. [lower case letters]

ii. Onset and Duration – Last paragraph:

Intramuscular doses, in a range of 9...

iii. Note – First paragraph, last sentence:

"Sodium Chloride (0.9%) Injection" rather than "[redacted]

h. HOW SUPPLIED

i. Delete reference to the [redacted] and [redacted] strengths.

ii. Delete the statement "[redacted]" and see the comment under TITLE.

i. ANIMAL PHARMACOLOGY AND TOXICOLOGY

i. Interaction with...medication:

"Medication" rather than "medication" [upper case "M"]

ii. Blood pressure – Second paragraph, penultimate sentence:

...support the hypothesis... [rather than "[redacted]

iii. Metabolic Disposition – First paragraph, second sentence:

...lower concentrations were found in the heart... [delete "[redacted]

iv. Please note 21 CFR 201.1(h)(2) states that "the appearance on a drug product label of a person's name without qualification is a representation that the named person is the sole manufacturer". We note that "Bioniche Pharma (Canada) Ltd." appears without qualification. Since "Bioniche Pharma (Canada) Ltd." is the distributor of this drug product per your container labels, include one of the qualifying statements found in 21 CFR 201.1(h)(5) or (6).

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling review branch.html

APPEARS THIS WAY
ON ORIGINAL

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and ex

/s/

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