CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-974

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 74-974 Date of Submission: October 1, 1996

Applicant's Name: Akorn, Inc.

Established Name: Lorazepam Injection USP, 2 mg/mL (1 mL Syringe)

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Storage Statement

      i. Revise to include the following temperature range:

         ...2° - 8°C (36° - 46°F).

      ii. Revise to include the following sentence immediately after the "Protect from light" statement:

         Use carton to protect contents from light.

   b. Revise statement of contents to read:

      1 mL fill in 2 mL syringe to be consistent with innovator label.

2. CONTAINER (1 mL Syringe)

   a. See GENERAL COMMENTS (a) and (b).

   b. Revise to include 0.5 mL and 1.5 mL calibrations.

   c. Revise the routes of administration to appear as follows:

      FOR IM USE
      FOR IV ROUTE SEE DIRECTIONS

3. CARTON (10 x 1 mL Sterile Syringe Units)

   a. See GENERAL COMMENTS (a) and (b).

b. Revise the routes of administration to appear as follows:

For IM Injection
For IV use, additional dilution is required; see enclosed information.

c. Revise to include the following:

Each syringe contains excess space of approximately 1 mL to permit mixture with other compatible medicaments before injection.

d. Revise the "Each mL contains" statement to include the quantity or proportion of the inactive ingredients. You are referred to 21 CFR 201.100(b)(5)(iii) for further guidance.

4. INSERT

a. GENERAL COMMENT

It is noted that you have combined the package insert for your proposed lorazepam injection syringe (74-974) and vial (74-025) products, as does the reference listed drug. Please note that if both ANDAs are not approved at the same time, it may be necessary to revise your labeling.

b. DESCRIPTION

i. Revise the first sentence of the first paragraph to read:

Lorazepam Injection, USP is a sterile solution. Lorazepam is a benzodiazepine with antianxiety and sedative effects intended for intramuscular or intravenous routes of administration. It has the following chemical name: 7-chloro...

ii. Revise to include the molecular formula.

iii. Revise the molecular weight to read, 321.16 as per USP 23.

iv. Revise so that the following sentence immediately precedes the "Each mL contains" statement:

Lorazepam is a nearly white powder almost insoluble in water.

v. See CARTON comment (d). Also, refer to 21 CFR 201.57(a)(iii).

c. CLINICAL PHARMACOLOGY (PHARMACOKINETICS)

Revise the first sentence to read,

Lorazepam injection is...

d. INDICATIONS AND USAGE

Revise the ultimate sentence to read,

...(see "**PRECAUTIONS** - INFORMATION FOR PATIENTS").

e. WARNINGS

Revise the sixth paragraph to read,

...injectable lorazepam as premature...

f. PRECAUTIONS (PREGNANCY)

Revise subsection heading to read,

PREGNANCY
Teratogenic Effects. Pregnancy Category D.

g. OVERDOSAGE

Revise to add the following as the ultimate paragraph:

The benzodiazepine antagonist flumazenil may be used in hospitalized patients as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert including "**CONTRAINDICATIONS**," "**WARNINGS**," and "**PRECAUTIONS**" should be consulted prior to use.

h. DOSAGE AND ADMINISTRATION

i. ADMINISTRATION

Revise the ultimate paragraph to read,

...Dextrose Injection USP, 5%.

ii. Revise to add the following as the ultimate subsection:

DIRECTIONS FOR DILUTION FOR IV USE FOR PREFILLED SYRINGES

To dilute, adhere to the following procedure:

1. Extrude the entire amount of air in the half-filled syringe.
2. Slowly aspirate the desired volume of diluent.
3. Pull back slightly on the plunger to provide additional mixing space.
4. Immediately mix contents thoroughly by gently inverting syringe repeatedly until a homogenous solution results. Do not shake vigorously, as this will result in air entrapment.

i. HOW SUPPLIED

i. Revise the second and third lines to read:

2 mg/mL; 1 mL fill in a 2 mL prefilled syringe; 22 gauge x 1-1/4 Inch Needle

2 mg/mL; 1 mL fill in a 2 mL vial

ii. Revise the fourth line to read:

Lorazepam Injection, USP...

iii. "STORAGE" is not a section heading. Revise format so that it does not appear as such.

iv. See GENERAL COMMENTS (a).

Please revise your labels and labeling, as instructed above, and submit in final print, or draft if you prefer.

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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 explained.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

FEB 19 1997

Lorazepam Injection
2 mg/mL
ANDA #74-974
Reviewer: Moo Park
Filename: 74974w.o96

Akorn
Decatur, IL
Submission Date:
October 1, 1996

Review of a Waiver Request

I. Objective

Review of Akorn's waiver request for its Lorazepam Injection, 2 mg/mL. The reference listed product is Wyeth-Ayerst's Ativan®, 2 mg/mL.

II. Comment

1. The test and reference products are injectable solutions in nonaqueous vehicle. Formulations for the test and reference products are identical. Test formulation is shown in Table 1.

Table 1. Test Formulation

Ingredient	Test Product, %w/w
Lorazepam,	
Benzyl Alcohol,	
Polyethylene Glycol	
Propylene Glycol,	

2. The waiver is granted.

III. Recommendation

The Division of Bioequivalence agrees that the information submitted by Akorn demonstrate that Lorazepam Injection, 2 mg/mL, falls under 21 CFR Section 320.22 (b) of the Bioavailability/ Bioequivalence Regulations. The waiver of *in vivo* bioequivalence

study for the 2 mg/mL strength of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation, 2 mg/mL strength, to be bioequivalent to Wyeth-Ayerst's Ativan^{R}, 2 mg/mL strength.

The firm should be informed of the recommendation.

Moo Park

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE Ramakant M. Mhatre 2/13/97
Ramakant M. Mhatre, Ph.D.
Team Leader, Review Branch III
Division of Bioequivalence

Concur: _____ Date: 2/19/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

RECORD OF TELEPHONE CONVERSATION

10:30A

The T.con was in response to the amendment filed August 21, 1997. The applicant responded to the microbiology deficiencies regarding the media fill for the 2.25 cc syringes as presented in the letter dated June 12, 1997, Question #3

The applicant provided the syringe media fill. There were items not covered by the submission. Due to the age of the application, response time and the second [micro] reviewer, a clarification of these items was appropriate by Telephone Amendment. The questions are as follows:

Was there a growth promotion test for media used during the media fill?

How many units are filled, i.e., the batch was written in Liters, not units?

How does the media fill time compare to actual production time, e.g., downtime simulation: breaks, stoppages and repairs, etc.?

JB said he would attempt to gather staff to answer these questions this afternoon (after 1:00 PM EST) and resolve this as a Telephone Amendment.

DATE
3/12/98

ANDA NUMBER
74-974

IND NUMBER
n/a

TELECON

INITIATED BY	MADE
_ APPLICANT/ SPONSOR	_X_ BY TELE.
_X_ FDA IN PERSON	_

PRODUCT NAME
Lorazepam Injection USP

FIRM NAME
Taylor Pharmaceuticals

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
James Baumann, Jr. (JB) Regulatory Affairs

TELEPHONE NUMBER
(217) 423-9715

SIGNATURE
Andrew H. K.
3/12/98

RECORD OF TELEPHONE CONVERSATION

2:30P

Andrea S. High
Witness: James McVey

The T.con regarding the media fill continued when James Baumann (JB), Jr. Regulatory Affairs, returned the call with staff:

Lou Frasier, V.P. QA/QC
Rick Taylor, Regulatory Compliance
Charles Coates(CC), QA

The questions were asked in the earlier T.con (See 10:30 A, same date).

CC stated that the media fill was not as long as a production lot but did include stoppages, personnel, etc.. He also stated that the number of syringes filled during production was approx. The media fill was approx. units; however, the fill rate was much slower and considered "worst case". He believed that these issues were covered in the 4 pages of the early volumes of the application. I told JB to submit them as a Telephone Amendment followed by a hardcopy to the Document Room. CC also indicated that the duration and fill number for media fills as a true process simulation for production is under consideration.

DATE
3/12/98

ANDA NUMBER
74-974

IND NUMBER
n/a

TELECON

INITIATED BY _X **APPLICANT/ BY SPONSOR** **MADE** _X **TELE.**
_ **FDA** _ **IN PERSON**

PRODUCT NAME
Lorazepam Injection USP

FIRM NAME
Taylor Pharmaceuticals

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
See Text

TELEPHONE NUMBER
(217)423-9715

SIGNATURE