ANDA 74-648

MAR 13 1997

Roxane Laboratories, Inc.
Attention: Sue T. Bastaja, R.Ph., J.D.
P.O. Box 16532
Columbus, OH 43216

Dear Madam:

This refers to your abbreviated new drug application dated March 16, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Lorazepam Oral Solution, 0.5 mg/5 mL.

Reference is also made to your amendments dated January 15, April 25, October 16, 22, and 23, 1996, and January 8, February 5, 24, and 28, 1997.

We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The drug can be expected to have the same therapeutic effect as that of the reference listed drug product relied upon by the Agency for the basis of safety and effectiveness.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FDA-2253 at the time of their initial use.

Sincerely yours,

3/14/97

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

MAR 18

NDC 0054-8509-16

DELIVERS 10 mL

LORAZEPAM ℞ IV

Oral Solution

1 mg per 10 mL

Each 10 mL contains Lorazepam 1 mg

SUGAR FREE

Caution: Federal law prohibits dispensing without prescription.

Store at Cold Temperature–
Refrigerate 2°-8°C (36°-46°F).

Roxane Laboratories, Inc.
Columbus, Ohio 43216

4487455

PEEL
115

NDC 0054-8510-16

DELIVERS 20 mL

LORAZEPAM ℞ IV

Oral Solution

2 mg per 20 mL

Each 20 mL contains Lorazepam 2 mg

SUGAR FREE

Caution: Federal law prohibits dispensing without prescription.

Store at Cold Temperature–
Refrigerate 2°-8°C (36°-46°F).

Roxane Laboratories, Inc.
Columbus, Ohio 43216

4487460

PEEL
115

NDC 0054-3509-63

500 mL

C IV

LORAZEPAM
Oral Solution

0.5 mg per 5 mL

SUGAR FREE

Each 5 mL contains: Lorazepam 0.5 mg.

Dispense in tight, light-resistant container as defined in the USP/NF. Protect from light.

Store at Cold Temperature - Refrigerate 2°-8°C (36°-46°F)

USUAL DOSAGE: See Package Insert for Complete Prescribing Information.

Caution: Federal law prohibits dispensing without prescription.

N 3 0054-3509-63 4

LOT
EXP.

4120690

Roxane Laboratories, Inc. Columbus, Ohio 43216

115

NDC 0054-8508-16

DELIVERS 5 mL

LORAZEPAM
Oral Solution
0.5 mg per 5 mL

C IV

Each 5 mL contains Lorazepam 0.5 mg

SUGAR FREE

Caution: Federal law prohibits dispensing without prescription.

Store at Cold Temperature–Refrigerate 2°-8°C (36°-46°F).

Roxane Laboratories, Inc. Columbus, Ohio 43216

4487450

PEEL

115

NDC 0054-3509-58

240 mL

CIV

LORAZEPAM
Oral Solution

0.5 mg per 5 mL

SUGAR FREE

Each 5 mL contains:
Lorazepam 0.5 mg

USUAL DOSAGE: See Package Insert for Complete Prescribing Information.

Caution: Federal law prohibits dispensing without prescription.

Roxane Laboratories, Inc.
Columbus, Ohio 43216

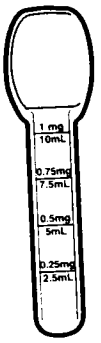
4120685

115

Pharmacist: Do Not Remove This Panel

NURSE/PATIENT:
Please note diagram below. Fill the spoon to the level of the prescribed dose

PROTECT FROM LIGHT



LOT
EXP.

Dispense in tight, light-resistant container as defined in the USP/NF. Protect from light.

Store at Cold Temperature - Refrigerate 2°-8°C (36°-46°F)

NDC 0054-
3509-58

240 mL BOTTLE
and SPOON

C IV

LORAZEPAM
Oral Solution

0.5 mg per 5 mL

SUGAR FREE

Each 5 mL contains:
Lorazepam 0.5 mg.

USUAL DOSAGE: See Package Insert for Complete Prescribing Information.

Dispense in a tight, light-resistant container as defined in the USP/NF.

Protect from light.

Caution: Federal law prohibits dispensing without prescription

Store at Cold Temperature–Refrigerate
2°- 8°C (36°- 46°F)

Roxane
Laboratories, Inc.
Columbus, Ohio 43216—

3 0054-3509-58 0

125

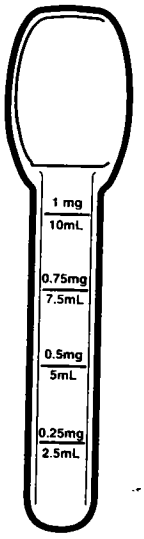
5716610

NDC 0054-
3509-58

240 mL BOTTLE
and SPOON

**PHARMACIST/
NURSE:**

Please note diagram to
the right. ▶
Fill the spoon to the level of
the prescribed dose.

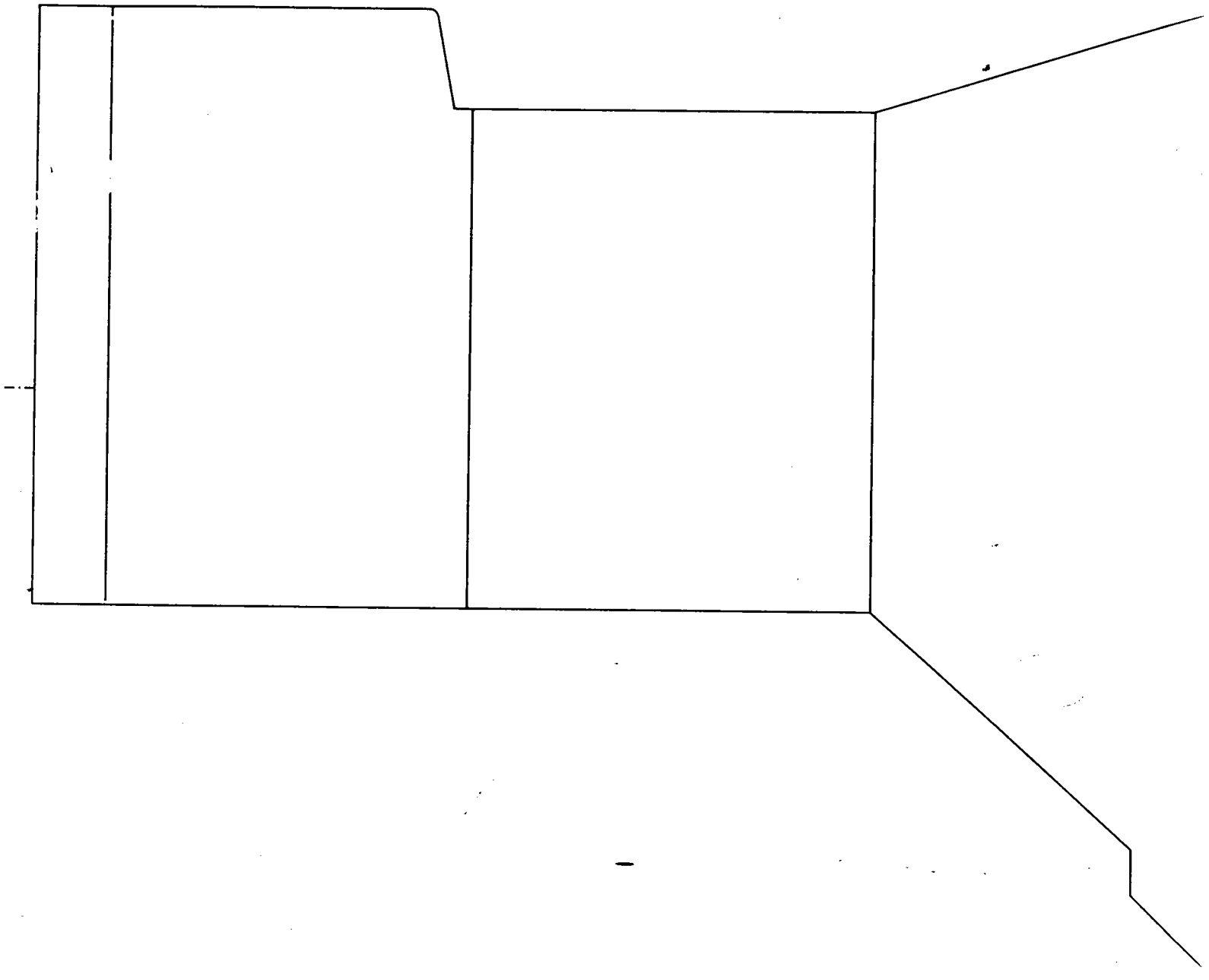


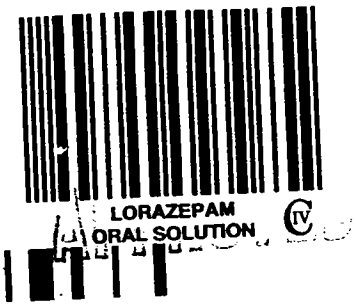
PROTECT FROM LIGHT

LORAZEPAM
Oral Solution C IV

0.5 mg per 5 mL

Roxane
Laboratories, Inc.
Columbus, Ohio 43216





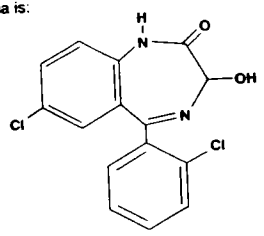
ROXANE LABORATORIES, INC.

LORAZEPAM ORAL SOLUTION CIV
0.5 mg per 5 mL

DESCRIPTION

Each 5 mL of Oral Solution contains:
Lorazepam ..... 0.5 mg

Lorazepam, an antianxiety agent has the chemical formula: 7-chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one. The molecular weight is 321.16. The structural formula is:



$C_{15}H_{10}Cl_2N_2O_2$

Lorazepam is a white or practically white, practically odorless powder, insoluble in water, sparingly soluble in alcohol, slightly soluble in chloroform.

Each 5 mL of Lorazepam Oral Solution, to be taken orally, contains 0.5 mg of lorazepam. *Inactive ingredients* are: polyethylene glycol, saccharin sodium, propylene glycol, and vanilla flavor.

CLINICAL PHARMACOLOGY

Studies in healthy volunteers show that in single high doses lorazepam has a tranquilizing action on the central nervous system with no appreciable effect on the respiratory or cardiovascular systems.

Lorazepam is readily absorbed with an absolute bioavailability of 90 percent. Peak concentrations in plasma occur approximately one hour following administration. The peak plasma level of lorazepam from a 2 mg dose is approximately 20 ng/mL.

The mean half-life of unconjugated lorazepam in human plasma is about 12 hours and for its major metabolite, lorazepam glucuronide, about 18 hours. At clinically relevant concentrations, lorazepam is approximately 85% bound to plasma proteins. Lorazepam is rapidly conjugated at its 3-hydroxy group into lorazepam glucuronide which is then excreted in the urine. Lorazepam glucuronide has no demonstrable CNS activity in animals.

The plasma levels of lorazepam are proportional to the dose given. There is no evidence of accumulation of lorazepam on administration up to six months.

Studies comparing young and elderly subjects

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The plasma levels of lorazepam are proportional to the dose given. There is no evidence of accumulation of lorazepam on administration up to six months.

Studies comparing young and elderly subjects have shown that the pharmacokinetics of lorazepam remain unaltered with advancing age.

INDICATIONS AND USAGE

Lorazepam is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety or anxiety associated with depressive symptoms.

Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

The effectiveness of lorazepam in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Lorazepam is contraindicated in patients with known sensitivity to the benzodiazepines or with acute narrow-angle glaucoma.

WARNINGS

Lorazepam is not recommended for use in patients with a primary depressive disorder or psychosis. As with all patients on CNS-acting drugs, patients receiving lorazepam should be warned not to operate dangerous machinery or motor vehicles and that their tolerance for alcohol and other CNS depressants will be diminished.

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (See DRUG ABUSE AND DEPENDENCE section).

PRECAUTIONS

In patients with depression accompanying anxiety, a possibility for suicide should be borne in mind.

For elderly or debilitated patients, the initial daily dosage should not exceed 2 mg in order to avoid oversedation.

Lorazepam dosage should be terminated gradually, since abrupt withdrawal of any anti-anxiety agent may result in symptoms similar to those for which patients are being treated: anxiety, agitation, irritability, tension, insomnia, and occasional convulsions.

The usual precautions for treating patients with impaired renal or hepatic function should be observed.

In patients where gastrointestinal or cardiovascular disorders coexist with anxiety, it should be noted that lorazepam has not been shown to be of a significant benefit in treating the gastrointestinal or cardiovascular component.

Esophageal dilation occurred in rats treated with lorazepam for more than one year at 6 mg/kg/day. The no-effect dose was 1.25 mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10 mg per day). The effect was reversible only when the treatment was withdrawn within two months of first observation of the phenomenon. The clinical significance of this is unknown. However, use of lorazepam for prolonged periods and in geriatric patients requires caution, and there should be frequent monitoring for symptoms of upper G.I. disease.

Information for Patients: To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

Essential Laboratory Tests: Some patients on lorazepam have developed leukopenia, and some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver-func-

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Essential Laboratory Tests: Some patients on lorazepam have developed leukopenia, and some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver-function tests are recommended for patients on long-term therapy.

Clinically Significant Drug Interactions: The benzodiazepines, including lorazepam, produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

Carcinogenesis and Mutagenesis: No evidence of carcinogenic potential emerged in rats during an 18-month study with lorazepam. No studies regarding mutagenesis have been performed.

Pregnancy: Reproductive studies in animals were performed in mice, rats, and two strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all of these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

The clinical significance of the above findings is not known. However, an increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) during the first trimester of pregnancy has been suggested in several studies. Because the use of these drugs is rarely a matter of urgency, the use of lorazepam during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should

be considered. Patients should be advised that if they become pregnant, they should communicate with their physician about the desirability of discontinuing the drug.

In humans, blood levels obtained from umbilical cord blood indicate placental transfer of lorazepam and lorazepam glucuronide.

Nursing Mothers: It is not known whether oral lorazepam is excreted in human milk like the other benzodiazepine tranquilizers. As a general rule, nursing should not be undertaken while a patient is on a drug, since many drugs are excreted in human milk.

Pediatrics Use: Safety and effectiveness of lorazepam in pediatric patients of less than 12 years have not been established.

ADVERSE REACTIONS

Adverse Reactions, if they occur, are usually observed at the beginning of therapy and generally disappear on continued medication or upon decreasing the dose. In a sample of about 3500 anxious patients, the most frequent adverse reaction to lorazepam is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%), and unsteadiness (3.4%). Less frequent adverse reactions are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, together with various gastrointestinal symptoms and autonomic manifestations. The incidence of sedation and unsteadiness increased with age.

Small decreases in blood pressure have been noted but are not clinically significant, probably being related to the relief of anxiety produced by lorazepam.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

DRUG ABUSE AND DEPENDENCE

Lorazepam Oral Solution is classified by the Drug Enforcement Administration as a schedule IV controlled substance.

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (e.g., convulsions, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuance of lorazepam. The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed.

Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving lorazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

OVERDOSAGE

In the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken. Manifestations of lorazepam overdosage include somnolence, confusion, and coma. Induced vomiting and/or gastric lavage should be undertaken, followed by general supportive care, monitoring of vital signs, and close observation of the patient. Hypotension, though unlikely, usually may be controlled with norepinephrine bitartrate injection. The usefulness of dialysis has not been determined.

Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation, and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for re-sedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. **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.

DOSAGE AND ADMINISTRATION

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DOSAGE AND ADMINISTRATION

Lorazepam is administered orally. For optimal results, dose, frequency of administration, and duration of therapy should be individualized according to patient response.

The usual range is 2 to 6 mg/day given in divided doses, the largest dose being taken before bedtime, but the daily dosage may vary from 1 to 10 mg/day.

For anxiety, most patients require an initial dose of 2 to 3 mg/day given b.i.d. or t.i.d.

For insomnia due to anxiety or transient situational stress, a single daily dose of 2 to 4 mg may be given, usually at bedtime.

For elderly or debilitated patients, an initial dosage of 1 to 2 mg/day in divided doses is recommended, to be adjusted as needed and tolerated.

The dosage of lorazepam should be increased gradually when needed to help avoid adverse effects. When higher dosage is indicated, the evening dose should be increased before the daytime doses.

HOW SUPPLIED

Lorazepam Oral Solution is available as a clear, uncolored, vanilla-flavored solution.

NDC 0054-8508-16: Unit Dose Patient Cups™ filled to deliver 5 mL (0.5 mg lorazepam), ten 5 mL Patient Cups™ per shelf pack, four shelf packs per shipper.
NDC 0054-8509-16: Unit Dose Patient Cups™ filled to deliver 10 mL (1 mg lorazepam), ten 10 mL Patient Cups™ per shelf pack, four shelf packs per shipper.
NDC 0054-8510-16: Unit Dose Patient Cups™ filled to deliver 20 mL (2 mg lorazepam), ten 20 mL Patient Cups™ per shelf pack, four shelf packs per shipper.
NDC 0054-3509-58: Bottles of 240 mL with calibrated patient spoon.
NDC 0054-3509-63: Bottles of 500 mL.

Dispense in tight, light-resistant container as defined in the USP/NF.

PROTECT FROM LIGHT

Store at Cold Temperature–
Refrigerate 2°-8°C (36°-46°F)

Caution: Federal law prohibits dispensing without prescription.

4055810 **Revised November 1995**
115

Roxane
Laboratories, Inc.
Columbus, Ohio 43216

APPROVAL PACKAGE SUMMARY FOR 74-648

ANDA: 74-648

FIRM: Roxane Laboratories, Inc.

DRUG: Lorazepam

DOSAGE: Solution

STRENGTH: 1 mg/10 mL

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 10/22/96

BIO STUDY/BIOEQUIVALENCE STATUS: Bioequivalence study has been found acceptable 1/13/97 by Hoainhon Nguyen

METHODS VALIDATION: The methods validation is acceptable 12/21/95

STABILITY: The firm has submitted satisfactory accelerated stability data for three months at 25°C and 24 months at 4°C (labeled storage condition) for the product in 8 ounce amber glass bottles, 500 mL HDPE bottles and unit dose cups.

LABELING REVIEW STATUS: The labeling is satisfactory 2/23/96

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has submitted copies of two executed batch records; for lot # 939097 (bioequivalence lot) and lot # 949059 using drug substance manufactured by The DMF is satisfactory by
The intended production batch sizes will be using the same drug substance manufacturer, the same manufacturing procedure and the same equipment.

COMMENTS: The application is approvable.

REVIEWER: Nashed E. Nashed, Ph.D. DATE: 3/5/97

3/5/97

Supervisor: Paul Schwartz, Ph.D.

3/6/97

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 74-648

3. NAME AND ADDRESS OF APPLICANT

Roxane Laboratories, Inc.
P.O. Box 16532
Columbus, Ohio 43216

4. LEGAL BASIS FOR SUBMISSION

The firm indicated that to the best of their knowledge there are no patents that claim the listed drug. Patent 4017616 which is listed in the Orange Book expired on April 12, 1994 and claimed the injectable form of Lorazepam.

The application for Lorazepam Oral Solution, 0.5 mg/mL was submitted based on petition filed on May 27, 1994, and amendments dated June 16 and August 3, 1994 which was approved according to our letter dated February 7, 1995.

7. NONPROPRIETARY NAME

Lorazepam

9. AMENDMENTS AND OTHER DATES:

Original 3/16/95
Amendment 1/15/96
Amendment 4/25/96
Amendment 10/16/96
Amendment 10/22/96
Amendment 10/23/96
Amendment 1/8/97
Amendment 2/5/97
Amendment 2/24/97
Amendment 2/28/97

10. PHARMACOLOGICAL CATEGORY

Anti-anxiety

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

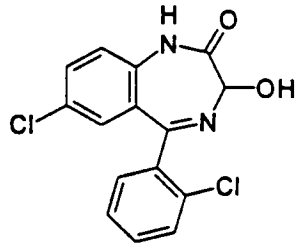
Solution

14. POTENCY

1 mg per 10 mL

15. CHEMICAL NAME AND STRUCTURE

Lorazepam. $C_{15}H_{10}Cl_2N_2O_2$. 321.16. 2*H*-1,4-Benzodiazepin-2-one, 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-, (±)-. 846-49-1. Tranquilizer (minor). USP 23, page 903.



16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable

19. REVIEWER:

Nashed E. Nashed, Ph.D.

DATE COMPLETED:

3/6/97
3/5/97

Supervisor: Paul Schwartz, Ph.D.

DEC 12 1995

Lorazepam Oral Solution
1 mg/10 mL oral solution
ANDA #74-648
Reviewer: James D. Henderson
File: 74648SD.395

Roxane Laboratories
Columbus, OH
Submitted:
March 16, 1995

REVIEW OF A COMPARATIVE BIOAVAILABILITY STUDY

I. Background

1. On 5/26/94 the sponsor filed a Suitability Petition (Docket #94P-0199/CP1) requesting FDA to make a determination of ANDA suitability for lorazepam oral solution, 1 mg/10 mL.

2. The petition was approved 2/7/95 as a new dosage form. The reference listed drug (RLD) in the petition was Ativan® tablets (Wyeth-Ayerst).

3. The sponsor has submitted an ANDA for its test product lorazepam oral solution 1 mg/10 mL comparing the test product with Ativan® 2 mg tablets in a "bioequivalence study". Because the test and reference products are not pharmaceutically equivalent, the submission should be referred to as a comparative bioavailability study. If the results from this study for 90% CI's meet current DBE requirements, it may be stated that the test product can be expected to have the same therapeutic effect as the RLD.

II. Study Design

This was a single dose, randomized, two-way crossover bioavailability study comparing equal doses (2 mg) of the test product lorazepam oral solution 1 mg/10 mL (Roxane) with the RLD Ativan® 2 mg tablets (Wyeth-Ayerst) in healthy male subjects under fasting conditions with at least one week washout. Serum concentrations of lorazepam were measured.

Sequence 1: Subjects 1,3,5,8,10,11,13,15,18,19,21,24,26
Sequence 2: Subjects 2,4,6,7,9,12,14,16,17,20,22,23,25

III. Study Site

Clinical and Analytical Site:

Medical Director:
Scientific Director:
Protocol #: 10494 (3/3/93); IRB approval 3/11/93; finalized 10494B, 1/17/94
Study #: 025-52-10494
Study Dates: Period I, 1/21-24/94 (dosing on 1/23); Period II, 1/28-31/94 (dosing on 1/29)
Analysis Dates: 2/14/94 to 3/27/94 (64 days)

IV. Subject Selection

Twenty-six subjects were enrolled (24 subjects plus 2 alternates). The protocol stated that samples from all subjects who complete the study were to be analyzed.

A. Inclusion Criteria

- male, 18-50 years old
- within ± 15% of ideal weight for height (Metropolitan Life Insurance Company Statistical Bulletin, 1983)
- good health as determined by medical history, physical examination, and laboratory tests (variations from established normal ranges may be acceptable if clinically insignificant and do not compromise safety)

B. Exclusion Criteria

- history of or ongoing serious organ, systemic, or psychiatric disease
- history of alcohol or drug abuse
- known allergy to lorazepam or other benzodiazepines
- positive urine drug and alcohol screen at check-in prior to each phase
- minimum screening and/or check-in BP and pulse rate of 100/60 mm Hg and 55 bpm, respectively
- consumption of Rx drugs within 14 days of first dosing
- consumption of OTC medications within 7 days of first dosing (excluding OTC analgesics, vitamins, medicated lozenges, and non-ingested medications)

V. Study Procedures

Both treatments were administered with 240 mL of water. For Treatment A (test), the 20 mL dose (= 2 mg) was drawn and measured in a 30-mL syringe. Each syringe was weighed before and after it was filled with the 20-mL dose, with no rinsing. After the dose was given, the syringe was weighed again.

In Period 1, the weight of the dose ranged from 21.339-21.673 g (mean, 21.446 g, CV 0.4%). In Period 2, the weight of the dose ranged from 21.325-21.56 g (mean, 21.454 g, CV 0.4%).

A. Treatments

1) Trt. A (test), lorazepam oral solution 1 mg/10 mL, dose = 2 mg (20 mL), Roxane lot #939097, potency 100.7%; manufactured 12/93

2) Trt. B (RLD), Ativan® 2 mg tablet, dose = 2 mg (1 tablet), Wyeth-Ayerst lot #9920489 (exp 7/94), potency 102.8%

B. Restrictions

Subjects were confined at the clinical site from 12 hours before dosing until 24 postdose, and instructed to return for the 36- and 48-hour samples. Smoking was not allowed from one hour prior to four hours after dosing, or within one hour of scheduled BP readings. Subjects remained seated for four hours postdose, then were allowed to ambulate freely. No strenuous physical activity was allowed at the clinical site. Alcohol and caffeine consumption were prohibited from 24 hours and 12 hours, respectively, prior to dosing in each phase.

C. Meals and Fluids

Fasting occurred for at least 10 hours predose until five hours postdose when standardized meals were begun. Water was allowed freely except within one hour of dosing.

D. Blood Sampling

Venous blood (15 mL) samples were collected in Vacutainers® with no anticoagulant at 0 (predose), 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 12, 18, 24, 36, and 48 hours postdose. Samples remained at room temperature for about 30 minutes for clot formation, centrifuged at 2500 rpm for 30 min at 10°, and the serum was separated and stored frozen in labeled tubes at -20° pending assay.

E. Monitoring

BP and pulse rate were measured after the subject was seated at least three minutes, at 0 (predose), 1, 2, 4, and 24 hours postdose. Interphase use of ℞ and OTC medications and alcohol was documented.

VI. Analytical Methodology

VIII. Results

A. Product Information

1. Formulation of the test product: Table 1

2. Dissolution of the RLD: Table 2

3. Potencies: within =

B. Clinical

1. Completion:

Twenty-five subjects completed the crossover. Subject #15 did not return to the clinical site for Period 2 and was withdrawn.

2. Protocol Deviations:

a. blood sampling

There were three late samples in Period 2. In two of these cases, the actual time differed by > 5% from the scheduled time, and AUC was calculated using actual times; these results differed by < 0.2% from the AUC using scheduled times (in final report). There was one missing sample (S20, Per.1, 36 hr).

b. restrictions

Subjects #3 and #17 consumed alcoholic beverages during washout periods. The reviewer concurs these deviations are unlikely to affect the study outcome.

3. Adverse Events:

Trt. A: There were 30 reported events involving 21 subjects. All events were judged to be of mild severity with one exception (S8, lightheaded, moderate severity), and judged to be possibly or probably related to the administered drug. No drug treatment was

required in any case and all events resolved spontaneously. Events: lightheaded (5), sleepy or drowsy (15), mellow feeling (2), unbalanced (1), diaphoretic (2), double vision (2), headache (1), nausea (1), unpleasant taste (1).

Trt. B: There were 23 reported events involving 19 subjects. All events were judged to be of mild severity, and judged to be possibly or probably related to the administered drug. No drug treatment was required in any case and all events resolved spontaneously. Events: lightheaded (5), sleepy or drowsy (12), mellow feeling or relaxed (3), double vision (1), vomiting (1), heavy eyelids (1).

C. Pharmacokinetics/Statistics

1. Mean serum lorazepam concentrations from the test product and RLD are shown in Table 3. There were ten cases where the volume of sample was insufficient for analysis: predose sample for Subjects 1, 2, and 3 in both periods; and, S2 at 2, 12, 18, and 24 hours. There were no reported predose concentrations or instances of CMAX as the first nonzero concentration.

2. Mean reported pharmacokinetic parameters for lorazepam are shown in Table 4. Statistically significant treatment effects ($p < 0.05$) were noted for logAUC0-T, CMAX, and logCMAX.

3. T/R ratios are shown in Table 5.

4. The sponsor excluded S2 from the data analysis because of missing assay results over a wide selection of the concentration-time profile after Trt. B. Twenty-four data sets were used in the analysis.

5. The sponsor could not estimate KE in four cases: Trt. A, S1 and S23; Trt. B, S1 and S22. Consequently, only 22 values of AUCINF could be analyzed from each treatment.

D. Analytical

1. During study validation

IX. Comments

1. Using the data on diskette supplied by the sponsor, the reviewer performed ANOVA with the GLM procedure of SAS and obtained results for 90% CI's of log-transformed AUC and CMAX identical to the sponsor's reported results.

2. The reviewer repeated the analysis including the data for Subject 2. The resulting 90% CI's were: logAUCT, 102.3-116.5; logAUCI, 100.2-109.8; logCMAX, 110.0-126.9.

3. For KE, the sponsor reported six values with an $R^2 < 0.9$ in addition to the four inestimable cases. The reviewer repeated the 90% CI calculation for logAUCINF with all ten of the values for AUCINF above excluded from the analysis. The resulting 90% CI was 98.2-105.0; with S2 excluded, 98.2-105.0.

4. The reviewer applied the following criteria to the QC samples: 1) 4/6 samples should have determined values within ± 20% of nominal for the Low QC and within ± 15% for the Middle and High QC's; 2) at least one sample from each concentration range should be acceptable. All 27 curves met these criteria.

5. The reviewer applied the following criteria to standard curves: 1) for the 2 and 5 ng/mL standards, the back-calculated values should be within ± 20% of nominal; 2) for the remaining standards, back-calculated values should be within ± 15% of nominal; 3) at least 5/6 standards from each curve should meet these criteria. All 27 curves met these criteria.

6. Long-term frozen stability was determined as follows: Serum samples spiked with known concentrations of lorazepam (5 and 30 ng/mL) were prepared on 3/3/94 and stored at -20° with the study samples. These stability samples were assayed at the same time as the study samples, and also on 5/12/94 (10 weeks).

It is apparent from the data reported by the sponsor that only two samples were assayed at each concentration on 5/12/94. The Crystal City Conference Report (12/90) on analytical validation[1] stated that "the stability of the analyte in the biological matrix at the intended storage temperature(s) should be established" without recommending a minimum number of replicates. For accuracy and precision, a minimum of five samples at each concentration was recommended.

7. For autosampler stability, the sponsor reported for a single standard curve from the original injection and reinjected 24

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[1] Shah VP, Midha KK, Dighe SV, et al. Analytical methods validation: bioavailability, bioequivalence, and pharmacokinetic studies. J Pharm Sci 1992;81:309-12.

hours later. This data is unacceptable since it consists of only a single sample at six concentrations at only one time during the run.

8. Twenty samples were reassayed: pharmacokinetic anomaly, 15; processing error, 3; concentration above highest standard, 2.

For all 15 samples reassayed as PK anomalies, duplicate reassay determinations were made, and the median value reported (note: the median value was one of the duplicate reassay values in 13 cases; the original value was the median in 2 cases).

In two cases, the determined concentration was above the range of the standard curve. These samples were diluted and reassayed. However, details of the dilution procedure and validation data were not provided.

9. The sponsor provided chromatograms from Subjects 3, 9, 12, 16, and 20:

- Predose samples and ST7 samples (0 ng/mL standard) contained only IS peaks with no evidence of analyte.
- The standards and QC samples from all submitted runs showed a large, potentially interfering peak eluting immediately before the much smaller IS peak. In some cases, the IS peak elutes on the descending shoulder of the large extraneous peak.

10. The sponsor used a weighting factor of $1/CONC^2$ for evaluation of standard curve parameters. Using the approach of Bolton[2] to examine whether a weighted linear regression is required, the reviewer used the raw PHR data from all of the standard curves as follows:

- For each standard concentration (CONC), the mean PHR, SD, CV, variance ($\sigma = SD^2$), and INVVAR ($= 1/\sigma$) were calculated.
- Heterogeneity of variance is demonstrated if either the variance of the dependent variable mean PHR (σ_{MPHR}) or the standard deviation (SD) is proportional to the independent variable (CONC).
- From the REG procedure of SAS, the R^2 value for σ_{MPHR} vs. CONC was 0.9651, indicating good correlation. If σ is proportional to mean PHR, then 1/CONC or 1/PHR might be an appropriate weighting factor.

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[2] Bolton S. Pharmaceutical statistics: practical and clinical applications. 2nd ed. New York: Marcel Dekker, Inc., 1990:234-5.

- The R^2 value for SD vs. CONC was 0.9967 (strong correlation), and the R^2 values for CV vs. MPHR and CV vs. CONC were 0.7037 and 0.676, respectively (weaker correlations, but slope was significantly different from zero, $p < 0.05$), indicating a constant CV model. For the constant CV model, $1/CONC^2$ or $1/PHR^2$ might be an appropriate weighting factor.

- The weighting factor should be inversely proportional to variance. The R^2 values for INVVAR ($= 1/\sigma$) vs. 1/CONC (WF1), $1/CONC^2$ (WF2), 1/PHR (WF3), and $1/PHR^2$ (WF4) were 0.9617, 0.9997, 0.9362, 0.9984, respectively, suggesting that WF2 ($1/CONC^2$) and WF4 ($1/PHR^2$) have the strongest inverse correlations with variance.

- The R^2 values for MPHR vs. CONC were $\geq$ 0.9977 for the weighting factors 1/CONC, $1/CONC^2$, 1/PHR, and $1/PHR^2$.

- The reviewer's results show that the data appear to be described by a constant CV model, and that the weighting factors $1/CONC^2$ and $1/PHR^2$ should be acceptable.

X. Deficiencies

1. Since the ANDA for the test product was filed as a result of an approved Suitability Petition, the criterion for approval is that the test product must have the same therapeutic effect as the RLD upon which the petition is based. One approach towards meeting this criterion is to perform a comparative bioavailability study and to demonstrate that the pharmaceutically inequivalent test product and RLD achieve the statistical criteria for bioequivalence of two products.

Based on the sponsor's reported data and the reviewer's analysis, the upper limit of the 90% confidence interval for log-transformed CMAX exceeds the allowed limit of 125% of the reference product mean. Therefore, the DBE concludes that the results of this comparative bioavailability study do not achieve the statistical criteria for bioequivalence. The DBE has no other criteria upon which to base a decision as to whether the test product lorazepam oral solution 1 mg/10 mL will have the same therapeutic effect as the RLD Ativan® 2 mg tablets.

2. Regarding the analytical data:

a. long-term frozen stability: Only two samples were assayed at each concentration on 5/12/94. This part of validation should be repeated using a minimum of six samples at each concentration.

b. In two cases where samples were reassayed, the determined concentration was above the range of the standard curve. These samples were diluted and reassayed. Please provide complete details of the dilution procedure and validation data (with dates

included) that was performed at the time of this study.

c. The autosampler stability data should be repeated with at least six replicates at each of at least three concentrations.

d. The standards and QC samples from all submitted runs showed a large, potentially interfering the In some cases, the Please provide complete details and explanations regarding the criteria for resolution of the

XI. Recommendations

1. As stated in deficiency comment #1, this comparative bioavailability study fails to meet the current statistical criteria for bioequivalence, and the DBE has no other basis upon which to state that the test product and RLD are expected to have the same therapeutic effect. However, there are two alternatives:

a. The study may be reviewed by the Acting Director, Office of Generic Drugs, who may conclude, based on clinical judgment, that the test product and RLD will have the same therapeutic effect.

b. A consult opinion may be obtained from the appropriate medical reviewing division in the Office of Drug Evaluation.

2. The bioavailability study conducted by Roxane Laboratories on its lorazepam oral solution 1 mg/10 mL, lot #939097, comparing it to Ativan® 2 mg tablet, lot #9920489, has been found incomplete by the Division of Bioequivalence due to deficiency #2.

3. The sponsor should be informed of deficiency comment #2a-d and recommendation #2.

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK 11/24/95

Concur Date 12/12/95
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

Table 1 - Formulation of the Test Product

FOR INTERNAL USE ONLY

Ingredient	amount per 10 mL
lorazepam USP	1.0 mg
polyethylene glycol 400 NF	
saccharin sodium USP (Saccharin Soluble)	
propylene glycol USP	
vanilla artificial	

Table 2 - Dissolution Testing Results

Drug (Generic Name): lorazepam
Dose Strength: 2 mg tablet
ANDA No.: 74-648
Firm: Roxane
Submission Date: 3/16/95
File Name: 74648SD.395

I. Dissolution Testing (USP Method):

USP 23 Basket: X Paddle: RPM: 100
No. Units Tested: 12
Medium: water Volume: 500 mL
Specifications: NLT NLT min
Reference Drug: Ativan® (Wyeth-Ayerst)
Assay Methodology: USP XXII (HPLC)

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product N/A Lot # Strength (mg)			Reference Product Ativan® Lot #9920489 Strength (mg) 2		
	Mean %	Range	%CV	Mean %	Range	%CV
15	-	-	-	100		2.1
30	-	-	-	102		1.4
45	-	-	-	103		1.7
60	-	-	-	104		1.1

Table 3 - Mean Reported Serum Lorazepam Concentrations (ng/mL, N = 24)

Time (hr)	Trt. A (mean)	(test) CV(%)	Trt. B (mean)	(ref.) cv(%)	% Diff.
0	0.00	-[1]	0.00	-[1]	-
0.33	11.27	67	6.41	91	75.82
0.67	25.51	47	17.92	55	42.35
1	26.08	33	20.83	42	25.2
1.5	22.46	27	21.52	34	4.368
2	21.49	25	21.72	28	-1.06
2.5	20.16	25	20.47	28	-1.51
3	18.65	26	19.25	31	-3.12
4	17.24	23	17.87	25	-3.53
6	16.38	28	17.00	29	-3.65
12	11.92	31	11.79	35	1.103
18	8.67	35	8.06	32	7.568
24	6.12	34	6.20	39	-1.29
36	4.80	108	3.29	58	45.9
48	1.78	114	1.67	127	6.587

[1] N = 22

Trt. A = lorazepam oral solution, 2 mg (20 mL), Roxane
Trt. B = Ativan® 2 mg tablet, Wyeth-Ayerst

Table 4 - Mean Reported Pharmacokinetic Parameters (N = 24)

Parameter[1]	Trt. A (mean)[2]	test CV(%)	Trt. B (mean)	ref. CV(%)	[3]	90% CI
AUC0-T						
Arith.	397.58	38	372.56	34	6.72	-
LSM	397.58	-	372.56	-	1.067	100.4-113.0
logAUC0-T	-	-	-	-	1.06	101.5-110.6
AUCINF[4]						
Arith.	455.28	152	431.01	33	5.63	-
LSM	462	-	443	-	1.043	100.0-108.4
logAUCINF	-	-	-	-	1.05	100.2-109.8
CMAX						
Arith.	29.26	33	24.47	28	19.57	-
LSM	29.26	-	24.47	-	1.196	111.4-127.8
logCMAX	-	-	-	-	1.18	109.4-127.0
TMAX (hr)	1.01	46	1.72	65	-41.3	-
KEL[4] (hr^{-1})	0.0483	32	0.0513	26	-5.85	-
HALF[4] (hr)	16.0	38	14.4	27	11.11	-

[1] units: AUC, ng*hr/mL; CMAX, ng/mL

[2] both arithmetic (Arith.) and least squares (LSM) means are reported

[3] For arithmetic means, the % difference is calculated as $(A_{mean} - B_{mean}) * 100/B_{mean}$. For LSM, the ratio A_{LSM}/B_{LSM} is calculated. For log-transformed values, the ratio of least squares geometric means is reported as exp(ESTIMATE) where the ESTIMATE is obtained from the ANOVA.

[4] N = 22

Trt. A = lorazepam oral solution, 2 mg (20 mL), Roxane
Trt. B = Ativan® 2 mg tablet, Wyeth-Ayerst

Table 5 - T/R Ratios

Subject	AUC0-T	AUCINF	CMAX
1			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
< 75%	0	0	1
75-125%	23	20	15
> 125%	1	1	8

OCT 1 1 1996

Lorazepam Oral Solution
1 mg/10 mL oral solution
ANDA #74-648
Reviewer: James D. Henderson
File: 74648SD.496

Roxane Laboratories
Columbus, OH
Submitted:
April 25, 1996

RESPONSE TO REVIEW OF A COMPARATIVE BIOAVAILABILITY STUDY

Background

1. On 5/26/94 the sponsor filed a Suitability Petition (Docket #94P-0199/CP1) requesting FDA to make a determination of ANDA suitability for lorazepam oral solution, 1 mg/10 mL. The petition was approved 2/7/95 as a new dosage form. The reference listed drug (RLD) in the petition was Ativan® tablets (Wyeth-Ayerst).

2. The sponsor submitted an ANDA ON 3/16/95 for its test product lorazepam oral solution 1 mg/10 mL comparing the test product with Ativan® 2 mg tablets in a "bioequivalence study". Because the test product is the subject of a Suitability Petition, the submission should be referred to as a comparative bioavailability study. If the results from this study met current DBE requirements for 90% CI's, it could be stated that the test product could be expected to have the same therapeutic effect as the RLD.

3. The study was reviewed and found incomplete (file date 12/12/95) with analytical deficiencies and the result that the 90% CI for log-transformed CMAX exceeded the allowed upper limit of equivalence (125% of reference product). The sponsor was informed of these deficiencies in a 2/26/96 letter and has responded to the comments in the present submission.

4. A consult was requested from the Division of Neuropharmacological Drug Products (HFD-120) on 1/24/96. The medical reviewer's (Paul J. Andreason, M.D.) comment was that it was impossible to make a judgement as to whether the solution dosage form was therapeutically equivalent to the tablet from the material in the application. Thomas Laughren, Group Leader, HFD-120, expressed the opinion that it cannot be concluded that the observed differences (between the two dosage forms) are of no importance. The Division Director of HFD-120, Paul Leber, M.D., stated that to answer the question of same therapeutic effect would require a predictive function linking response to BE parameters; the data was not available for this procedure. The consult was completed 4/8/96.

5. On 4/25/96 Mark Anderson, HFD-650 Project Manager, spoke with Dr. Andreason (transcript of conversation attached). Subsequently, it was discovered that, in error, only the first volume (no BA data) had been sent for consult review. However,

Dr. Andreason stated that the safety data from the study (ADR report) would probably not impact his decision.

6. On 5/8/96 the complete biostudy was forwarded again to HFD-120 for consult review. The completion of the consult and final conclusions are pending.

Responses to Deficiency Comments:

1. Deficiency Comment #1

> **From the letter: Since the ANDA for this test product was filed as a result of an approved Suitability Petition, the Office of Generic Drugs' criterion for approval is that the test product must have the same therapeutic effect as the RLD upon which the petition is based. Our review of the data has led us to conclude that the upper limit of the 90% confidence interval for log-transformed CMAX exceeds the allowed limit of 125% of the reference product mean. Therefore, the results of this comparative bioavailability study do not achieve the normal statistical criteria for bioequivalence. We have sent the study on consult to the Division of Neuropharmacology for a medical determination as to whether the difference in CMAX between test and RLD would be expected to cause a difference in therapeutic effect. Comments, if any, will be sent under separate cover when the consult is completed.**

Sponsor's Response: The small differences in CMAX should not produce a difference in therapeutic effect, and the minor differences are due to differences in dosage forms which are not clinically significant.

Reviewer's Comment: Completion of the consult review and conclusions is pending.

2. Deficiency Comment #2

> **The following comments pertain to the analytical data from the submitted study. Please provide responses to these comments but note that the bioequivalence portion of the application will remain incomplete pending a satisfactory resolution of the above referenced consult.**
>
> **a. Only two long-term frozen stability samples were assayed at each concentration on 5/12/94. This part of the validation should be repeated using a minimum of six samples at each concentration.**

b. In two cases where samples were reassayed, the determined concentration was above the range of the standard curve. These samples were diluted and reassayed. Please provide complete details of the dilution procedure and validation data (with dates included) that was performed at the time of this study.

c. The autosampler stability data should be repeated with at least six replicates at each of at least three concentrations.

d. The standards and QC samples from all submitted runs showed a large, potentially interfering

In some cases, the

Please provide complete details and explanations regarding the criteria for resolution of the

ns.

a. Sponsor's Response: Serum samples for frozen stability were analyzed on five occasions with a total of 19 assay results over 71 days. Samples (N = 2) at nominal lorazepam concentrations of 5 and 30 ng/mL (prepared on 3/3/94) were assayed on 3/5/94, 3/10/94, 3/21/94, 3/27/94, and 5/12/94 with CV's of 9.4 and 11.5%, respectively, and accuracies of 116% and 98.3%, respectively. There are no specific requirements regarding the number of replicates necessary for validation of frozen stability and these requirements have not been discussed in any industry conference or published by any regulatory source.

Reviewer's Comment: The first dosing in the study occurred on 1/23/94 and the last analysis date was 3/27/94 which corresponds to 63 days of frozen storage. (Note: In the 12/12/95 review, the reviewer stated 64 days.) The sponsor states that the amount of time required to cover both clinical and analytical portions of the study is 67 days.

The sponsor's frozen stability samples were prepared on 3/3/94 and last assayed on 5/12/94 for a total of 70 days (71 days as stated by the sponsor). The second to last assay date was 3/27/94 which corresponds to 24 days of frozen storage. Therefore, all of the frozen stability data reported by the sponsor from 3/5/94 through 3/27/94 is useless for validating frozen stability since it corresponds to a time interval less than the frozen storage period. The only applicable results are from 5/12/94, and as noted in the deficiency comment, there are only two replicates at two concentrations. Only four separate results are available to establish frozen stability.

The sponsor's last comment regarding the lack of an industry/agency requirement for the number of replicates is the

sponsor's only relevant argument. In one workshop report[1], it was recommended that five replicates should be used for method validation to establish accuracy and precision. The same report was silent with regard to the number of replicates for frozen stability determination.

It is the reviewer's opinion that the use of two replicates at a given concentration is not sufficient for frozen stability evaluation since a meaningful CV cannot be obtained, and since instability may not be detected from only two results at a given concentration.

b. Sponsor's Response: Samples were diluted by using 0.5 mL of sample and adding 0.5 mL of blank serum. Performing sample dilutions in this manner did not change the total amount of matrix used for the extraction procedure. Policies in effect at the time of this study did not require further validation work.

Reviewer's Comment: The response is unacceptable. No validation data for the dilution procedure was provided. The objective of the dilution procedure is to bring the determined concentrations of samples originally above the ULQ back within the standard curve range on reassay. Therefore, validation of the dilution procedure requires a reference QC sample with a nominal concentration above the ULQ which is then diluted back into the standard curve range. Validation of dilution methods should be done during assay of the study samples, immediately after the original assay value is shown to be above ULQ and before the reassay occurs.

c. Sponsor's Response: Standards were and then 24 hours later, and ratios from the two were compared. The % differences ranged from 4.29-10.2% and the mean difference was 6.86%. The reproducibility of these ratios proves the autosampler stability and there is no advantage to using more samples. There is no specific requirement regarding the number of replicates to demonstrate autosampler stability (note: the sponsor actually said "frozen stability" at this point) from any industry conference or any regulatory source.

Reviewer's Comment: By using only one sample at each standard concentration, the sponsor has precluded any determination of the precision of the measurements. If two had been made at each concentration would similar results have been obtained? If six were made at each concentration, or at least three concentrations, would an acceptable CV% been obtained? The sponsor has invoked the absence of any specific guideline for

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[1] Shah et al. Analytical methods validation: bioavailability, bioequivalence, and pharmacokinetic studies. J Pharm Sci 1992;81:309-12.

autosampler stability to justify only one sample at each concentration. The absence of any such guidelines is not an excuse for acceptability of analytical validation results based on only one replicate for any type of stability determination. In the reviewer's opinion, sufficient data is required to demonstrate an acceptable level of both precision and accuracy; this necessitates several replicates (6 suggested) at each concentration to generate a meaningful CV and to establish an acceptable range of accuracy for individual samples.

d. Sponsor's Response: Resolution was > 1.16 for all analytical runs and > 1.3 for most runs. This resolution is adequate for quantification of the IS.

Reviewer's Comment: The sponsor has not provided any documentation that its selection of values for resolution are accepted industry-wide or have any basis in the published literature.

Conclusions:

1. The sponsor response to deficiency comment #1 is acceptable since the consult review is still pending.

2. The sponsor's responses to deficiency comments #2a-d are unacceptable for the reasons stated in the following deficiency comments.

Deficiency Comments:

2a. All of the frozen stability data reported by the sponsor from 3/5/94 through 3/27/94 is not helpful for validating frozen stability since it corresponds to a time interval less than the frozen storage period during the study (67 days). The only applicable results are from 5/12/94 consisting of only two replicates at two concentrations. Since both precision and accuracy are required for all types of stability determinations, more replicates (6 suggested) at each concentration are essential for a meaningful CV and range of individual sample accuracies. The frozen stability validation study should be repeated using 6 replicates at two concentrations (Low and High QC's) over a frozen storage interval of 67 days. On both Days 0 (preparation of QC's) and Day 67, six individual values at each concentration should be obtained for comparison to nominal concentrations.

2b. No validation data for the dilution procedure was provided. The objective of the dilution procedure is to bring the determined concentrations of samples originally above the ULQ back within the standard curve range on reassay. Therefore, validation of the dilution procedure requires a reference QC sample with a nominal concentration above the ULQ which is then diluted back into the standard curve range. Validation of

dilution methods should be done during assay of the study samples, immediately after the original assay value is shown to be above ULQ and before the reassay occurs. Please provide validation data as described above using a sufficient number (6 suggested) of replicates to demonstrate precision and accuracy.

2c. Only one replicate at each concentration was used to determine autosampler stability. Since demonstration of both precision and accuracy are required for stability determinations, more replicates (6 suggested) at each concentration are essential for a meaningful CV and range of individual sample accuracies. The absence of specific, published industry or regulatory agency guidelines does not diminish the requirement for demonstration of an acceptable level of both precision and accuracy. The autosampler stability study should be repeated using 6 replicates at each of two concentrations (Low and High QC').

2d. The sponsor has not provided any documentation that its selection of values for resolution are accepted industry-wide or have any basis in the published literature.

Recommendations:

1. The bioavailability study conducted by Roxane Laboratories on its lorazepam oral solution 1 mg/10 mL, lot #939097, comparing it to Ativan® 2 mg tablet, lot #9920489, has been found incomplete by the Division of Bioequivalence due to deficiencies #2a-d.

2. The sponsor should be informed of deficiency comments #2a-d and recommendation #1.

3. Final determination of study acceptability will be made when the consult review is returned and the sponsor has successfully answered the comments 2a-d.

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR 5/30/96

Concur: _____ Date 10/11/96
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-648 SPONSOR : Roxane Labs
DRUG & DOSAGE FORM : Lorazepam Oral Solution
STRENGTH (s) : 1 mg/10ml
TYPE OF STUDY: SD ✓ SDF MULT OTHER
STUDY SITE: CLINICAL : ANALYTICAL : Same as Clinical

STUDY SUMMARY :

Parameter	test	ref	ratio	90% CI (log).
Cmax(ng/ml)	29.26	24.47	1.20	[1.09; 1.27]
AUC(0-T) ngxhr/ml	397.6	372.6	1.07	[1.02; 1.11]
AUC(0-Inf)ngxhr/ml	462	443	1.04	[1.00; 1.10]
Tmax hr	1.01	1.72		
Half-life hr	16.0	14.4		

DISSOLUTION :
Conditions

Time(min)	Test Mean(range)	Ref. Mean(range)
15	N/A	100 (96-104)
30		102 (100-105)
45		103 (100-106)

Q = NLT , NLT (USP)

PRIMARY REVIEWER : BRANCH : I

INITIAL : DATE : 1-24-97

BRANCH CHIEF : BRANCH : I

INITIAL : DATE : 1/24/97

Acting DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL : DATE : 1/27/97

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL : DATE : 1/26/97

ANDA 74-648

JAN 27 1997

Roxane Laboratories, Inc.
Attention: Sue T. Bastaja, R.Ph., J.D.
P.O. BOX 16532
Columbus OH 43216-6532

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Lorazepam Oral Solution 1 mg/10 mL.

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

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

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

JAN 17 1997

Lorazepam Oral Solution, 1 mg/10 ml
ANDA#74-648
Reviewer: Hoainhon Nguyen
WP#74648a.o96

Roxane Laboratories
Columbus, OH
Submission Date:
October 22, 1996
January 8, 1997

Review of a Study Amendment

The single-dose, two-way crossover bioavailability study comparing equal doses (2 mg) of the test product lorazepam oral solution 1 mg/10 ml (Roxane) with the RLD Ativan^{R} 2 mg tablets (Wyeth-Ayerst) was submitted March 16, 1995 and reviewed by Dr. James D. Henderson. The following deficiency comments by Dr. Henderson were sent to the firm on February 26, 1996.

1. Deficiency Comment #1

From the letter: Since the ANDA for this test product was filed as a result of an approved Suitability Petition, the Office of Generic Drugs' criterion for approval is that the test product must have the same therapeutic effect as the RLD upon which the petition is based. Our review of the data has led us to conclude that the upper limit of the 90% confidence interval for log-transformed CMAX exceeds the allowed limit of 125% of the reference product mean. Therefore, the results of this comparative bioavailability study do not achieve the normal statistical criteria for bioequivalence. We have sent the study on consult to the Division of Neuropharmacology for a medical determination as to whether the difference in CMAX between test and RLD would be expected to cause a difference in therapeutic effect. Comments, if any, will be sent under separate cover when the consult is completed.

2. Deficiency Comment #2

The following comments pertain to the analytical data from the submitted study. Please provide responses to these comments but note that the bioequivalence portion of the application will remain incomplete pending a satisfactory resolution of the above referenced consult.

a. Only two long-term frozen stability samples were assayed at each concentration on 5/12/94. This part of the validation should be repeated using a minimum of six samples at each concentration.

b. In two cases where samples were reassayed, the determined concentration was above the range of the standard curve. These samples were diluted and reassayed. Please provide complete details of the dilution procedure and validation data (with dates included) that was performed at the time of this study.

c. The autosampler stability data should be repeated with at least six replicates at each of at least three concentrations.

d. The standards and QC samples from all submitted runs showed a large,

Please provide complete details and explanations regarding the criteria for resolution of

Concerning Deficiency #1: Although Drs. Paul Andreason and Paul Leber of the Division of Neuropharmacology, when consulted, could not determine "as to whether the difference in CMAX between test and RLD would be expected to cause a difference in therapeutic effect" due to the lack of efficacy data, Dr. Roger Williams after consulting with Dr. Robert Temple further determined that the difference in CMAX between the test solution and reference tablet "should not be a

problem" and that OGD and DBE "can now proceed with the approval of ANDA 74-648" (See e-mail correspondence between OGD and the consulted division filed with the April 25, 1996 amendment). The consideration of bioequivalence between the test and reference products, therefore, is based on the statistical equivalence of the extent of absorption between the two products, as measured by AUC, and also on the "therapeutic equivalence" with respect to the rate of absorption of the two products, as measured by CMAX.

Concerning Deficiency #2: The firm has responded to the Deficiency Comment #2 on April 25, 1996. However, the responses were found not satisfactory by Dr. Henderson. Further telephone discussions between the firm and the DBE, as well as between the DBE and the analytical laboratory were carried out on June 26, July 31 and October 11, 1996 (See telephone records also attached to the amendment jacket). As the results of these telephone discussions, the firm has submitted the current amendment to re-address the Deficiency Comment #2 above of the original submission. Since his last review, Dr. Henderson has left the DBE. The amendment is now reassigned to this reviewer.

Response to Deficiency #2a:

The firm has clarified that "the period over which long term frozen stability data were obtained (70 days) is greater than the period over which samples were stored during this study (64 days)." and there was "a slight error in the counting of the time periods" which were reported in the original study submission.

Although Dr. Henderson found that duplicate of measurement at the first day of storage and at the last day was insufficient, this comment was not addressed further in any telephone discussion between DBE and the firm or the analytical laboratory. The record of the telephone discussions between Dr. Keith Chan of DBE and Mr. Don Chmielewski of Roxane on June 29, 1996, indicated that the agency will accept the number of measurement of this long-term stability study. However, 6 replicates are required if the stability study is to be repeated with duplicate of measurement at each of 3 control samples (low, medium and high). It should be noted that this requirement did not actually address the deficiency brought up by Dr. Henderson.

In addition, based on the long-term stability data as submitted by the firm, the difference in lorazepam plasma concentration between Days 70 and 0 was **+18%** for both control samples, 5 and 30 ng/ml (Means of 30 ng/ml of Day 0 and Day 70 were 27.95 and 33.10 ng/ml; means of 5 ng/ml of Day 0 and Day 70 were 5.61 and 6.62 ng/ml). **This difference is considered to be significant.** There was also an increase trend in the concentrations over the storage time.

On December 13, 1996, Mark Anderson and Lizzie Sanchez of the Division of Bioequivalence telephoned Elizabeth Lane of conveying the concern of the above apparent 18% increase in the lorazepam concentration in the long-term stability study and requesting an explanation for the data. On January 8, 1997, Roxane submitted the explanation provided by additional stability data to support the explanation.

believed that "The apparent increase in the lorazepam concentration for the latter time point is most likely the result of inter-assay variability in these samples and is not stability related." (It should be pointed out that Dr. Henderson had requested the stability data be given in replicate of 6 to verify the variability of the data and to determine whether the stability results are stability related.) In addition , submitted **the results of an additional long-term stability study** conducted on samples of approximately two years and four months frozen at -20°C. Three samples of each concentration of 5.00 ng/ml 30.0 ng/ml were analyzed at Day 0 (April 6, 1994) and Day 870 (August 23, 1996). The data showed that there was a difference of 5% and less in lorazepam concentration between two measurement dates. (See Review Attachment No. 6)

The explanation by the analytical laboratory is therefore considered satisfactory. The stability data are considered adequate.

<u>Response to Deficiency #2b:</u>

The details of the dilution procedure were provided. It was agreed during the July 31, 1996 telephone discussion that additional work would be as follows:

would make one concentration, dilute it six times (in the same manner), assay against a usual calibration line with the usual acceptance QC

samples."

Mean of the 60 ng/ml (with a 5 fold dilution) control was 65.9 ng/ml (CV% of 1.12 and accuracy of 109.8%).

The response is considered adequate.

Response to Deficiency #2c:

In addition to the data provided in the April 25, 1996 amendment (single measurement at each of 6 concentrations, before and after 24 hours), the firm was able to provide 6 more observations (duplicate measurement at each of 3 other concentrations, before and after 39 hours). There was a decrease in measured lorazepam concentration when samples are on the autoinjector for 24 or 39 hours (mean of 5 to 7% decrease). However, since "there is not a greater decrease in concentrations of samples left on the autoinjector for 39 hours compared to those left on the autoinjector for 24 hours.", the decrease observed is considered not significant and partly due to high variability in the assay itself.

The response is considered adequate.

Response to Deficiency #2d:

According to the record of the telephone discussion on June 29, 1996, the firm's explanation concerning this deficiency was found acceptable by DBE. No further review is necessary for this response.

In summary, all responses by the firm to the Deficiency Comments are addressed adequately.

Recommendations:

The bioavailability study conducted by Roxane Laboratories on its Lorazepam Oral Solution 1 mg/10 mL, lot #939097, comparing it to Ativan® 2 mg tablet, lot #9920489, has been found **acceptable** by the Division of Bioequivalence. (See the summary of the study results in the Review Attachment Nos. 1 through 5)

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG _____ 1/13/97

Concur: _____ Date: 1/17/97
Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA # 74-648 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File

Hnguyen/11-26-96/Revised 01-10-97/WP#74648a.o96

Attachments: 6 pages

samples."

Mean of the 60 ng/ml (with a 5 fold dilution) control was 65.9 ng/ml (CV% of 1.12 and accuracy of 109.8%).

The response is considered adequate.

Response to Deficiency #2c:

In addition to the data provided in the April 25, 1996 amendment (single measurement at each of 6 concentrations, before and after 24 hours), the firm was able to provide 6 more observations (duplicate measurement at each of 3 other concentrations, before and after 39 hours). There was a decrease in measured lorazepam concentration when samples are on the autoinjector for 24 or 39 hours (mean of 5 to 7% decrease). However, since "there is not a greater decrease in concentrations of samples left on the autoinjector for 39 hours compared to those left on the autoinjector for 24 hours.", the decrease observed is considered not significant and partly due to high variability in the assay itself.

The response is considered adequate.

Response to Deficiency #2d:

According to the record of the telephone discussion on June 29, 1996, the firm's explanation concerning this deficiency was found acceptable by DBE. No further review is necessary for this response.

In summary, all responses by the firm to the Deficiency Comments are addressed adequately.

Recommendations:

The bioavailability study conducted by Roxane Laboratories on its Lorazepam Oral Solution 1 mg/10 mL, lot #939097, comparing it to Ativan® 2 mg tablet, lot #9920489, has been found acceptable by the Division of Bioequivalence. (See the summary of the study results in the Review Attachment Nos. 1 through 5)

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Acting Director, Division of Bioequivalence

cc: ANDA # 74-648 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File

Hnguyen/11-26-96/Revised 01-10-97/WP#74648a.o96

Attachments: 6 pages

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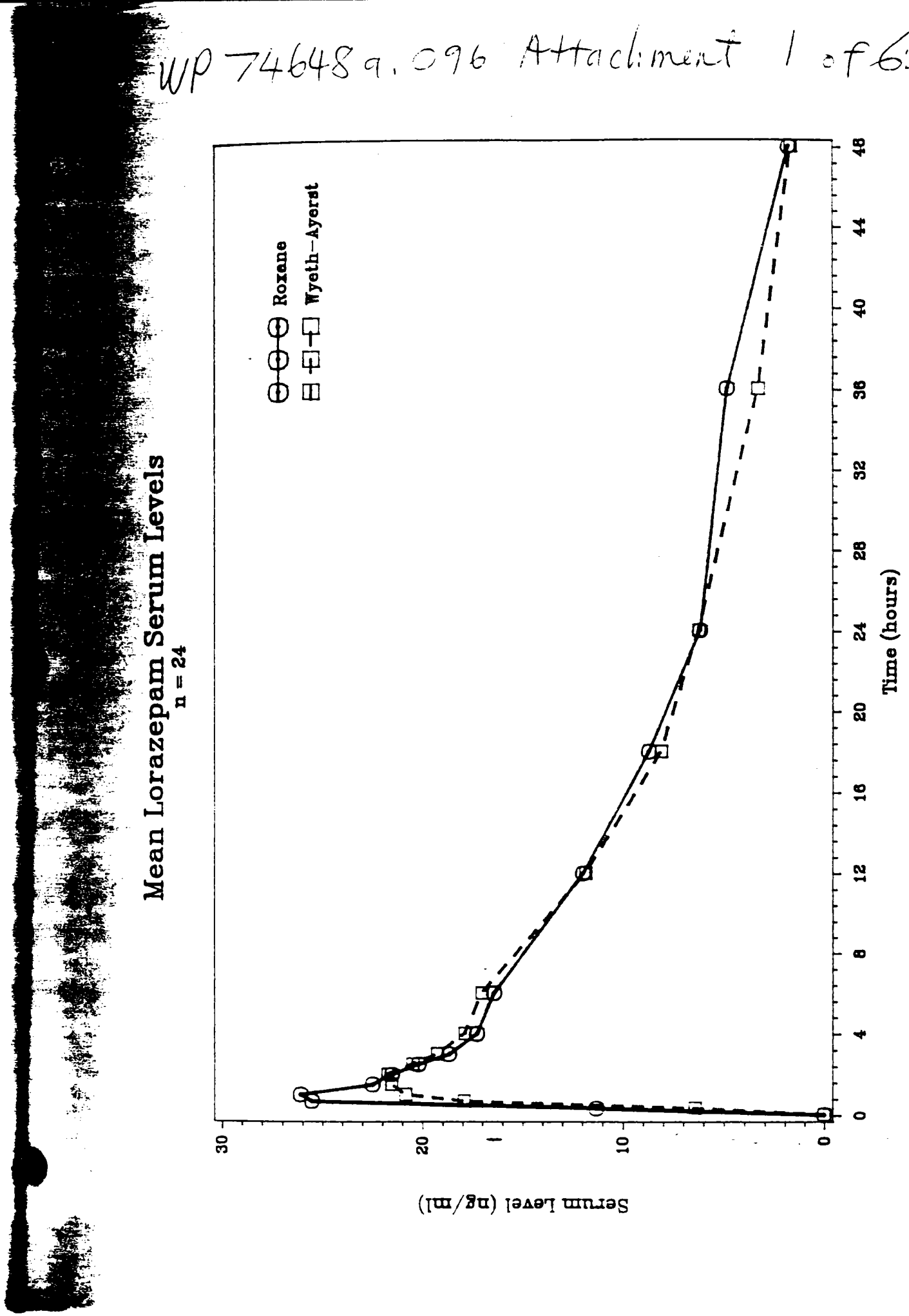

WF# 74648a.096 Attachment 2 of 6

Table 1 - Formulation of the Test Product

FOR INTERNAL USE ONLY

Ingredient	amount per 10 mL
lorazepam USP	1.0 mg
polyethylene glycol 400 NF	
saccharin sodium USP (Saccharin Soluble)	
propylene glycol USP	
vanilla artificial	

Table 2 - Dissolution Testing Results

Drug (Generic Name): lorazepam
Dose Strength: 2 mg tablet
ANDA No.: 74-648
Firm: Roxane
Submission Date: 3/16/95
File Name: 74648SD.395

I. Dissolution Testing (USP Method):

USP 23 Basket: X Paddle: RPM: 100
No. Units Tested: 12
Medium: water Volume: 500 mL
Specifications: NLT min, NLT min
Reference Drug: Ativan® (Wyeth-Ayerst)
Assay Methodology: USP XXII (HPLC)

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product N/A Lot # Strength (mg)			Reference Product Ativan® Lot #9920489 Strength (mg) 2		
	Mean %	Range	%CV	Mean %	Range	%CV
15	-	-	-	100		2.1
30	-	-	-	102		1.4
45	-	-	-	103		1.7
60	-	-	-	104		1.1

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Table 3 - Mean Reported Serum Lorazepam Concentrations (ng/mL, N = 24)

Time (hr)	Trt. A (test) (mean)	CV(%)	Trt. B (ref.) (mean)	CV(%)	% Diff.
0	0.00	-[1]	0.00	-[1]	-
0.33	11.27	67	6.41	91	75.82
0.67	25.51	47	17.92	55	42.35
1	26.08	33	20.83	42	25.2
1.5	22.46	27	21.52	34	4.368
2	21.49	25	21.72	28	-1.06
2.5	20.16	25	20.47	28	-1.51
3	18.65	26	19.25	31	-3.12
4	17.24	23	17.87	25	-3.53
6	16.38	28	17.00	29	-3.65
12	11.92	31	11.79	35	1.103
18	8.67	35	8.06	32	7.568
24	6.12	34	6.20	39	-1.29
36	4.80	108	3.29	58	45.9
48	1.78	114	1.67	127	6.587

[1] N = 22

Trt. A = lorazepam oral solution, 2 mg (20 mL), Roxane
Trt. B = Ativan® 2 mg tablet, Wyeth-Ayerst

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Table 4 - Mean Reported Pharmacokinetic Parameters (N = 24)

Parameter[1]	Trt. A (mean)[2]	test CV(%)	Trt. B (mean)	ref. CV(%)	[3]	90% CI
AUC0-T						
Arith.	397.58	38	372.56	34	6.72	-
LSM	397.58	-	372.56	-	1.067	100.4-113.0
logAUC0-T	-	-	-	-	1.06	101.5-110.6
AUCINF[4]						
Arith.	455.28	152	431.01	33	5.63	-
LSM	462	-	443	-	1.043	100.0-108.4
logAUCINF	-	-	-	-	1.05	100.2-109.8
CMAX						
Arith.	29.26	33	24.47	28	19.57	-
LSM	29.26	-	24.47	-	1.196	111.4-127.8
logCMAX	-	-	-	-	1.18	109.4-127.0
TMAX (hr)	1.01	46	1.72	65	-41.3	-
KEL[4] (hr^{-1})	0.0483	32	0.0513	26	-5.85	-
HALF[4] (hr)	16.0	38	14.4	27	11.11	-

[1] units: AUC, ng*hr/mL; CMAX, ng/mL

[2] both arithmetic (Arith.) and least squares (LSM) means are reported

[3] For arithmetic means, the % difference is calculated as $(A_{mean} - B_{mean}) * 100/B_{mean}$. For LSM, the ratio A_{LSM}/B_{LSM} is calculated. For log-transformed values, the ratio of least squares geometric means is reported as exp(ESTIMATE) where the ESTIMATE is obtained from the ANOVA.

[4] N = 22

Trt. A = lorazepam oral solution, 2 mg (20 mL), Roxane
Trt. B = Ativan® 2 mg tablet, Wyeth-Ayerst

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Table 5 - T/R Ratios

Subject	AUC0-T	AUCINF	CMAX
1			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
< 75%	0	0	1
75-125%	23	20	15
> 125%	1	1	8

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Long Term Stability Data for Lorazepam (-20°C) in Human Serum

Sample Preparation Date: 4/6/94

Theoretical Concentration (ng/mL)	4/6/94 Zero Hour Concentration (ng/mL)	Concentration 2.3 Years Later 8/23/96 (ng/mL)
30.0	30.9	32.0
30.0	31.6	31.4
30.0	32.0	31.8
Mean Concentration	31.5	31.7
Standard Deviation	0.557	0.306
% C.V.	1.77	0.965
% of Zero Hour	N/A	101

Theoretical Concentration (ng/mL)	4/6/94 Zero Hour Concentration (ng/mL)	Concentration 2.3 Years Later 8/23/96 (ng/mL)
5.00	5.43	5.62
5.00	5.55	5.68
5.00	5.38	5.79
Mean Concentration	5.45	5.70
Standard Deviation	0.0874	0.0862
% C.V.	1.60	1.51
% of Zero Hour	N/A	105