CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

74-278

Generic Name: Levorphanol Tartrate Tablets, USP

Sponsor: Roxane Larboratories, Inc.

Approval Date: March 31, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-278

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-278

APPROVAL LETTER

ANDA 74-278

MAR 31 2000

Roxane Laboratories, Inc.
Attention: Ann M. Maloney
P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Madam:

This is in reference to your abbreviated new drug application dated November 24, 1992, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Levorphanol Tartrate Tablets USP, 2 mg.

Reference is also made to your amendments dated August 13, 1996, April 29, June 9, and September 5, 1997; and November 10, 1999.

We have completed the review of this abbreviated 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 Division of Bioequivalence has determined your Levorphanol Tartrate Tablets USP, 2 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Levo-Dromoran® Tablets, 2 mg, of ICN Pharmaceuticals, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, 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 and 314.98. 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-40). Please do not use Form FD-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-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 8/31/00

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-278

APPROVED FINAL LABELING

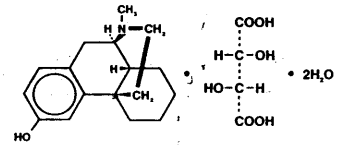
037 4055209

ROXANE LABORATORIES, INC.

LEVORPHANOL TARTRATE TABLETS USP CII 2 mg

DESCRIPTION

Levorphanol tartrate dihydrate is a potent narcotic analgesic with a molecular formula of $C_{17}H_{23}NO \cdot C_4H_6O_6 \cdot 2H_2O$ and molecular weight 443.5. Each mg of levorphanol tartrate dihydrate is equivalent to 0.58 mg levorphanol base. Levorphanol's chemical name is levo-3-hydroxy-N-methylmorphinan with the following structural formula, and has 3 asymmetric carbon atoms and the possibility of cis-trans isomerism:



Levorphanol tartrate dihydrate is a white crystalline powder, soluble in water and ether but insoluble in chloroform.

Each tablet, for oral administration, contains 2 mg levorphanol tartrate dihydrate. In addition, each tablet contains anhydrous lactose, corn starch, stearic acid, magnesium stearate and talc.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Levorphanol is a potent synthetic opioid similar to morphine in its actions. Like other μ-agonist opioids it is believed to act at receptors in the periventricular and periaqueductal gray matter in both the brain and spinal cord to alter the transmission and perception of pain. Onset of analgesia and peak analgesic effect following administration of levorphanol are similar to morphine and other drugs of this class when administered at equianalgesic doses.

Levorphanol produces a degree of respiratory depression similar to that produced by morphine at equianalgesic doses, and like many μ-opioid drugs, levorphanol produces euphoria or has a positive effect on mood in many individuals.

As with other opioids, the blood levels required for analgesia are determined by the opioid tolerance of the patient, and are likely to rise with chronic use. The rate of development of tolerance is highly variable, and is determined by the dose, dosing interval, age, use of concomitant drugs and physical status of the patient. While blood levels of opioid drugs may be helpful in assessing individual cases, dosage is usually adjusted by careful clinical observation of the patient.

Pharmacokinetics

The pharmacokinetics of levorphanol have been studied in a limited number of cancer patients following intravenous (IV), intramuscular (IM) and oral (PO) administration. Following IV administration plasma levels of levorphanol decline in a triexponential manner with a terminal half-life of 11-16 hours and a clearance of 0.75-1.0 L/kg/hr. Based on terminal half-life, steady-state plasma levels should be achieved by the second day of dosing. Levorphanol undergoes rapid (<1 hr) distribution and redistribution phases following IV administration and has a steady-state volume of distribution of from 10-13 L/kg. In vitro studies of protein binding indicate that levorphanol is only 40% bound to plasma proteins.

No pharmacokinetic studies of the absorption of IM levorphanol are available, but data from preoperative studies of a 2 mg IM dose in 1500 patients suggests

patient, and are likely to [illegible]
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No pharmacokinetic studies of the absorption of IM levorphanol are available, but data from preoperative studies of a 2 mg IM dose in 1500 patients suggests that absorption is rapid with onset of effects within 15-30 minutes of administration.

Levorphanol is well absorbed after PO administration with peak blood levels occurring 1 hour after dosing. The extent of first-pass metabolism of levorphanol is not well defined, but is likely to lie within the range of 30-70% based on a comparison of blood levels after oral and parenteral administration. The relative bioavailability of levorphanol tablets compared to IM or IV administration is not known.

Plasma levels of levorphanol following chronic administration in cancer patients were proportional to dose, but the analgesic effect was dependent on the degree of opioid tolerance of the patient. Expected steady-state plasma concentrations for a six-hour dosing interval can reach 2-5 times those following a single dose, depending on the patient's individual clearance of the drug. Very high blood levels of levorphanol can be reached with chronic use due to the long half-life of the drug and the development of tolerance. One study in 11 patients using the drug for control of cancer pain reported plasma concentrations from 5-10 ng/mL after a single 2 mg dose up to 50-100 ng/mL after repeated oral doses of 20-50 mg/day.

Levorphanol is extensively metabolized in the liver and is eliminated as the glucuronide metabolite. This renally excreted inactive glucuronide metabolite accumulates with chronic dosing in plasma at concentrations that reach five-fold that of the parent compound.

The effects of age, gender, hepatic and renal disease on the pharmacokinetics of levorphanol are not known. As with all drugs of this class, patients at the extremes of age are expected to be more susceptible to adverse effects because of a greater pharmacodynamic sensitivity and probable increased variability in pharmacokinetics due to age or disease.

Effect on Respiration

Two mg of intravenous levorphanol tartrate depresses respiration to a degree approximately equivalent to that produced by 10-15 mg of intravenous morphine in man. Initial doses of levorphanol above 3 mg have been associated with serious respiratory depression in patients not tolerant to the effects of opioids and are not recommended. As with all drugs of this class, the initial dose of levorphanol should be reduced by 50% or more when the drug is given to patients with any condition affecting respiratory reserve or in conjunction with other drugs affecting the respiratory center. Subsequent doses should then be individually titrated according to the patient's response. Respiratory depression produced by levorphanol tartrate can be reversed by naloxone, a specific antagonist.

Cardiovascular Effects

The hemodynamic changes after the intravenous administration of levorphanol have not been studied in man, but clinically resemble those seen after morphine.

Clinical Trials

Clinical trials have been reported in the medical literature that investigated the use of levorphanol as a preoperative medication, as the narcotic component of nitrous-narcotic anesthesia, as a postoperative analgesic, and in the management of chronic pain due to malignancy. In each of these clinical settings levorphanol has been shown to be an effective analgesic of the μ-opioid type, and similar to morphine, meperidine, oxycodone, or fentanyl.

A single 2 mg dose of levorphanol tartrate was studied as a routine preoperative premedicant in a blinded 1500 patient trial of a number of synthetic opiates, and was found to provide sedation similar to that observed with 100 mg meperidine or 10 mg of methadone. Levorphanol was also tested in doses of 1.5-2 mg in three intra-operative trials in a total of 300 patients against morphine, meperidine and fentanyl, and the clinical course of anesthesia was found to be equivalent to that produced by other drugs of this class as evaluated by sequential analysis of the analgesic records.

Levorphanol has been studied in oral, IM and IV dosage forms in three trials in chronic cancer patients. As is usual in such trials the dosages were individualized to each patient's level of opioid tolerance, with starting doses of 2 mg twice a day having to be advanced by 50% or more within a few weeks of starting therapy. Studies of levorphanol both in animals and man indicate that the relative potency of levorphanol is approximately 4-8 times that of morphine, depending on the specific circumstances of use.

Individualization of Dosage

Accepted medical practice dictates that the dose of any opioid analgesic be appropriate to the degree of pain to be relieved, the clinical setting, the physical condition of the patient, and the kind and dose of concurrent medication.

Levorphanol has a long half-life similar to metha-

Levorphanol has been studied in oral, IM and IV dosage forms in three trials in chronic cancer patients. As is usual in such trials the dosages were individualized to each patient's level of opioid tolerance, with starting doses of 2 mg twice a day having to be advanced by 50% or more within a few weeks of starting therapy. Studies of levorphanol both in animals and man indicate that the relative potency of levorphanol is approximately 4-8 times that of morphine, depending on the specific circumstances of use.

Individualization of Dosage

Accepted medical practice dictates that the dose of any opioid analgesic be appropriate to the degree of pain to be relieved, the clinical setting, the physical condition of the patient, and the kind and dose of concurrent medication.

Levorphanol has a long half-life similar to methadone or other slowly excreted opioids, rather than quickly excreted agents such as morphine or meperidine. Slowly excreted drugs may have some advantages in the management of chronic pain. Unfortunately, the duration of pain relief after a single dose of a slowly excreted opioid cannot always be predicted from pharmacokinetic principles, and the inter-dose interval may have to be adjusted to suit the patient's individual pharmacodynamic response.

Levorphanol is 4-8 times more potent than morphine, has a longer half-life, is better absorbed, and may be less subject to first-pass metabolism. When converting a patient to levorphanol, the total daily dose of levorphanol should begin at 1/12 of the total daily dose of oral morphine that such patients would be expected to require and then adjusted on subsequent days to the patient's clinical response. If a patient is to be placed on fixed-schedule dosing (round the clock) with this drug, care should be taken to allow adequate time after each dose change (36-48 hours) for the patient to reach a new steady-state before a subsequent dose adjustment to avoid excessive sedation due to drug accumulation.

INDICATIONS AND USAGE

Levorphanol tartrate tablets are indicated for the management of pain where an opioid analgesic is appropriate.

CONTRAINDICATIONS

Levorphanol tartrate tablets are contraindicated in patients allergic to levorphanol.

WARNINGS

Respiratory Depression

Levorphanol, like morphine, may be expected to produce serious or potentially fatal respiratory depression if given in excessive dosage, too frequently, or if given in full dosage to compromised or vulnerable patients. This is because the doses required to produce analgesia in the general clinical population may cause serious respiratory depression in vulnerable patients. Safe usage of this potent narcotic requires that the dosage and dosage interval be individualized to each patient based on the severity of the pain, weight, age, diagnosis and physical status of the patient, and the kind and dose of concurrently administered medication.

PRECAUTIONS

Head Injury and Increased Intracranial Pressure

Levorphanol tartrate must be used with extreme caution and only if the benefits of use outweigh the potential risks in patients with head injury. This is because levorphanol, like other potent analgesics, may elevate cerebrospinal fluid pressure and can produce

effects (e.g. miosis) that obscure the clinical course.

Cardiovascular Effects

The use of this drug in acute myocardial infarction or in cardiac patients with myocardial dysfunction or coronary insufficiency should be limited because the effects of levorphanol on the work of the heart are unknown.

Pre-Existing Pulmonary Disease

Because levorphanol tartrate causes respiratory depression, it should be administered with caution to patients with impaired respiratory reserve or respiratory depression from some other cause (e.g., from other medication, uremia, or severe infection, bronchial asthma, obstructive respiratory conditions, or intra-pulmonary shunting).

Use in Liver Disease

The drug should be administered with caution to patients with extensive liver disease who may be vulnerable to excessive sedation due to increased pharmacodynamic sensitivity or impaired metabolism of the drug. Laboratory tests have not indicated that levorphanol tartrate otherwise affects preexisting hepatic impairment.

Biliary Surgery

The safety of levorphanol in biliary surgery has not been studied and its use is not recommended.

Use in Alcoholism or Drug Dependence

Levorphanol has an abuse potential as great as morphine, and the prescription of this drug in such patients must always balance the prospective benefits against the risk of abuse and dependence. The use of levorphanol in patients with a history of alcohol or other drug dependence, either active or in remission, has not been specifically studied.

Drug Interactions

Concomitant use with other CNS agents - The dose of levorphanol should be reduced by about 50% or more when administered concomitantly with phenothiazines, droperidol, hydroxyzine, and other tranquilizers that potentiate the action of opioids. Concurrent use of levorphanol tartrate with all central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in additive central nervous system depressant effects. Although no interaction between MAO inhibitors and levorphanol has been observed, it is not recommended for use with MAO inhibitors.

Most cases of serious or fatal adverse events involving levorphanol reported to the manufacturer or the FDA have involved either the administration of large initial doses of the drug to non-opioid tolerant patients, or the simultaneous administration of levorphanol with other drugs affecting respiration (see WARNINGS). The initial dose of levorphanol should be reduced by approximately 50% or more when it is given to patients along with another drug affecting respiration.

Use in Ambulatory Patients

Levorphanol has been used in both inpatient and outpatient settings, but both physicians and patients must be aware of the risk of orthostatic hypotension, dizziness and syncope in ambulatory patients.

As with other opioids the use of levorphanol may impair mental and/or physical abilities required for the performance of potentially hazardous tasks or for the exercise of normal good judgement and patients and staff should be advised accordingly.

Concurrent use of levorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in additive central nervous system depressant effects.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No information about the effects of levorphanol on carcinogenesis, mutagenesis, or fertility is available.

Pregnancy

Pregnancy Category C.

The use of levorphanol in pregnancy is not recommended as no information about the effects of the drug on animal or human reproduction is available.

Labor and Delivery

The safety of levorphanol in labor and delivery is unknown and its use is not recommended.

Nursing Mothers

Levorphanol is not recommended for use in nursing mothers as it is not known if levorphanol is secreted in pharmacologically active amounts in human milk.

Pediatric Use

Levorphanol is not recommended in children under the age of 18 years as the safety and efficacy of the drug in this population has not been established.

Geriatric Use

The initial dose of the drug should be reduced by 50% or more in the infirm elderly patient, even though there have been no reports of unexpected adverse events in older populations. All drugs of this class may be associated with a profound or prolonged effect in elderly patients for both pharmacokinetic and pharmacodynamic reasons and caution is indicated.

ADVERSE REACTIONS

In 4365 patients treated with levorphanol in controlled clinical trials, the type and incidence of side effects were those expected of an opioid analgesic, and no unforeseen or unusual toxicity was reported.

Drugs of this type are expected to produce a cluster of typical opioid effects in addition to analgesia, consisting of nausea, vomiting, altered mood and mentation, pruritus, flushing, dyskinesia, difficulties in urination, and biliary spasm. The frequency and intensity of these effects appears to be dose related and proportional to the relative potency of each opioid. Although listed as adverse events these are expected pharmacologic actions of these drugs and should be interpreted as such by the clinician.

The incidence of adverse effects with levorphanol is based on data obtained from patients treated in controlled clinical trials and the unpooled [illegible]

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The incidence of adverse effects with levorphanol is based on data obtained from patients treated in controlled clinical trials and the uncontrolled clinical use of the drug. The adverse effects are listed below by frequency of occurrence within the body system affected and reflect the actual frequencies of each adverse effect in patients who received levorphanol. There has been no attempt to correct for a placebo effect or to subtract the frequencies reported by placebo-treated patients.

The following adverse events have been associated with the use of levorphanol and have been attributed to its use:

Body as a Whole: abdominal pain**, dry mouth**.

Cardiovascular System: hypotension***, dysrhythmia** (bradycardia).

Digestive System: nausea****, vomiting***.

Nervous System: dizziness****, confusion***, lethargy***, abnormal dreams**, abnormal thinking**, nervousness**, drug withdrawal*, hypokinesia*, dyskinesia*.

Respiratory System: hypoventilation****.

Skin & Appendages: Pruritus****, urticaria***, rash**, injection site reaction*.

Special Senses: abnormal vision**.

Urogenital System: difficulty urinating**.

(****) >10%
(***) 3-9%
(**) 1-3%
(*) <1%

DRUG ABUSE AND DEPENDENCE

(Schedule II Controlled Substance)
Warning: May be Habit Forming

All drugs of this class (pure μ-opioids of the morphine type) are habit forming and should be stored, prescribed, used, and disposed of accordingly.

Discontinuation of levorphanol after chronic use has been reported to result in withdrawal syndromes, and some reports of overuse and self reported addiction have been received. Neither withdrawal nor withdrawal symptoms are expected in postoperative patients who used the drug for less than a week or in patients who are tapered off the drug over 1-2 weeks after longer use.

OVERDOSAGE

Most reports of overdosage known to the manufacturer and to the FDA involve three clinical situations. These are: 1) the use of larger than recommended doses, 2) administration of the drug to children or small adults without any reduction in dosage, and 3) the use of the drug in ordinary dosage in patients compromised by concurrent illness.

As with all oral narcotics, overdose can occur due to accidental or intentional misuse of this product, especially in infants and children who may gain access to the drug in the home. Based on its pharmacology, levorphanol overdosage would be expected to produce signs of respiratory depression, cardiovascular failure (especially in predisposed patients), and/or central nervous system depression.

Treatment

The specific treatment of suspected levorphanol tartrate overdosage is immediate establishment of an adequate airway and ventilation, followed (if necessary) by intravenous naloxone. The respiratory and cardiac status of the patient should be continuously monitored and appropriate supportive measures instituted, such as oxygen, intravenous fluids, and/or vasopressors if required. Physicians are reminded that the duration of levorphanol action far exceeds the duration of action of naloxone, and repeated dosing with naloxone may be required.

DOSAGE AND ADMINISTRATION

Oral

The usual recommended starting dose for oral administration is 2 mg. This may be repeated in 3-6 hours as needed, provided the patient is assessed for signs of hypoventilation and excessive sedation. The effective daily dosage range, depending on the severity of the pain, is 8-16 mg in 24 hours in the non-tolerant patient. Total daily doses of more than 16 mg are generally not recommended as starting doses in non opioid tolerant patients.

Use in Chronic Pain

The dosage of levorphanol tartrate in cancer patients or in other conditions where chronic opioid therapy is indicated must be individualized (see CLINICAL PHARMACOLOGY, Individualization of Dosage). Since levorphanol is 4-8 times as potent as morphine and less subject to first pass metabolism, the daily dose of levorphanol should be estimated at about 1/12 the daily oral morphine dose, but may require prompt individualization of dosage owing to intra-individual differences in clearance and opioid tolerance.

Note: As with all controlled substances, abuse by health care personnel is possible and the drug should be handled accordingly.

HOW SUPPLIED

Levorphanol Tartrate Tablets USP, 2 mg
White, scored tablets (Identified 54 410).
NDC 0054-8494-24: Unit dose, 25 tablets per card (reverse numbered), 4 cards per shipper.
NDC 0054-4494-25: Bottles of 100 tablets.

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NDC 0054-4494-25: Bottles of 100 tablets.

Store at Controlled Room Temperature
15°-30°C (59°-86°F).

DEA Order Form Required

Caution: Federal law prohibits dispensing without prescription.

4055209 **Revised March 1997**
037

Roxane Laboratories, Inc.
Columbus, Ohio 43216

PRECAUTIONS

Head Injury and Increased Intracranial Pressure

Levorphanol tartrate must be used with extreme caution and only if the benefits of use outweigh the potential risks in patients with head injury. This is because levorphanol, like other potent analgesics, may elevate cerebrospinal fluid pressure and can produce

This Package Not For Household Use

USUAL DOSAGE: See Package Insert for Complete Prescribing Information

Store at Controlled Room Temperature 15°-30°C (59°-86°F)

Dispense in a tight container as defined in the USP/NF.

TABLETS IDENTIFIED 54 410

(Side One) 54 410 (Side Two)

DO NOT USE UNLESS TABLETS CARRY THIS IDENTIFICATION

NDC 0054-4494-25

100 Tablets

2 mg

LEVORPHANOL

Tartrate

Tablets USP

[redacted]

Rx only

Roxane Laboratories, Inc.
Columbus, Ohio 43216

4178401
037

Exp. MAR 31 2000

APPROVED

Lot

N 3 0054-4494-25 0

REVERSE 25 CARD BLISTER LABELS:

N 0054-8494-24 **2** mg
LEVORPHANOL CII
Tartrate
Tablet USP 2 mg
LOT 950000 EXP. JAN. 1, 97
Roxane Columbus, OH 43216

N 0054-8494-24 **2** mg
LEVORPHANOL CII
Tartrate
Tablet USP 2 mg
LOT 950000 EXP. JAN. 1, 97
Roxane Columbus, OH 43216

N 0054-8494-24 **2** mg
LEVORPHANOL CII
Tartrate
Tablet USP 2 mg
LOT 950000 EXP. JAN. 1, 97
Roxane Columbus, OH 43216

N 0054-8494-24 **2** mg
LEVORPHANOL CII
Tartrate
Tablet USP 2 mg
LOT 950000 EXP. JAN. 1, 97
Roxane Columbus, OH 43216

N 0054-8494-24 **2** mg
LEVORPHANOL CII
Tartrate
Tablet USP 2 mg
LOT 950000 EXP. JAN. 1, 97
Roxane Columbus, OH 43216

N 0054-8494-24 **2** mg
LEVORPHANOL CII
Tartrate
Tablet USP 2 mg
LOT 950000 EXP. JAN. 1, 97
Roxane Columbus, OH 43216

APPROVED

MAR 31 2000

NDC 0054-8494-24 25 Tablets (Reverse Numbered)

2 mg CII

LEVORPHANOL

Tartrate

[redacted]

0054-8494-24

TABLETS IDENTIFIED
54 410

Roxane Laboratories, Inc.
Columbus, Ohio 43216

4023600 055

MAR 31 2000

RETURNED DOSE POCKET

1 2 3 4 5

6 7 8 9 10

11 12 13 14 15

16 17 18 19 20

21 22 23 24 25

START

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-278

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO.1

2. ANDA # 74-278

3. NAME AND ADDRESS OF APPLICANT
Roxane Laboratories, Inc.
Attention: Donald H. Chmielewski
P.O. 16532
Columbus, OH 43216

4. LEGAL BASIS FOR ANDA SUBMISSION
LevoDromoran Tablets - Hoffman- LaRoche
Exp. date: December 19, 1991. Levo-Dromoran has no pending patents or periods of exclusivity.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Levorphanol Tartrate Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
November 24, 1992: Original submission.

FDA:
December 10, 1992: Acknowledgement letter.

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF#
DMF#
DMF#
DMF#
DMF#

13. DOSAGE FORM
Tablet

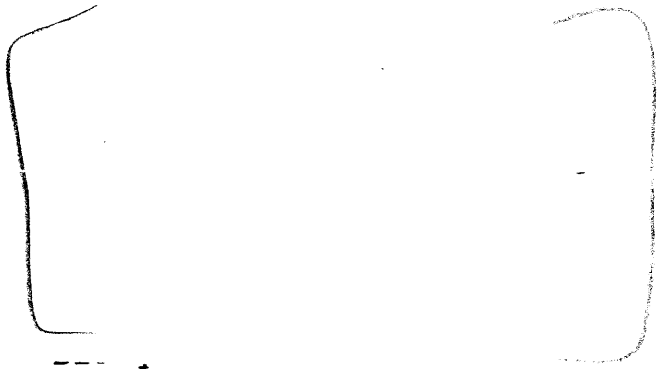
14. POTENCY
2 mg

15. CHEMICAL NAME AND STRUCTURE
17-Methylmorphinan-3-ol, tartrate (1:1) (salt) dihydrate.
$C_{17}H_{23}NO.C_4H_6O_6.2H_2O$ MW=443.49

See USP page 763 for chemical structure.

16. RECORDS AND REPORTS
N/A

17. COMMENTS



18. CONCLUSIONS AND RECOMMENDATIONS
This application is considered as not approvable. The letter will be issued. Also please see the comment under item 34 regarding the Bio batch.

19. REVIEWER:
Sema Basaran Ph.D.

DATE COMPLETED:
3-8-93

APPEARS THIS WAY
ON ORIGINAL

Redacted 10

pages of

trade secret and/or

confidential

commercial

information

1. CHEMIST'S REVIEW NO.2

2. ANDA # 74-278

3. NAME AND ADDRESS OF APPLICANT
Roxane Laboratories, Inc.
Attention: Donald H. Chmielewski
P.O. 16532
Columbus, OH 43216

4. LEGAL BASIS FOR ANDA SUBMISSION
LevoDromoran Tablets - Hoffman- LaRoche
Exp. date: December 19, 1991. Levo-Dromoran has no pending patents or periods of exclusivity.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Levorphanol Tartrate Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
November 24, 1992: Original submission.
June 16, 1995: amendment

FDA:
December 10, 1992: Acknowledgement letter.
June 2, 1993: Deficiency letter

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF#
DMF#
DMF#
DMF#
DMF#

13. DOSAGE FORM
Tablet

14. POTENCY
2 mg

15. CHEMICAL NAME AND STRUCTURE
17-Methylmorphinan-3-ol, tartrate (1:1) (salt) dihydrate.
$C_{17}H_{23}NO.C_4H_6O_6.2H_2O$ MW=443.49

See USP page 763 for chemical structure.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
The following deficiencies are noted in the review:

18. CONCLUSIONS AND RECOMMENDATIONS
This application is considered as not approvable. The letter will be issued.

19. REVIEWER: Sema Basaran Ph.D.

DATE COMPLETED: 10-31-95; 11-2-95

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DRV

1. CHEMIST'S REVIEW NO.3

2. ANDA # 74-278

3. NAME AND ADDRESS OF APPLICANT
Roxane Laboratories, Inc.
Attention: Donald H. Chmielewski
P.O. 16532
Columbus, OH 43216

4. LEGAL BASIS FOR ANDA SUBMISSION
LevoDromoran Tablets - Hoffman- LaRoche
Exp. date: December 19, 1991. Levo-Dromoran has no pending patents or periods of exclusivity.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Levorphanol Tartrate Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
November 24, 1992: Original submission.
June 16, 1995: amendment
April 29, 1997: Amendment

FDA:
December 10, 1992: Acknowledgment letter.
June 2, 1993: Deficiency letter
December 21, 1995: Deficiency letter

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic

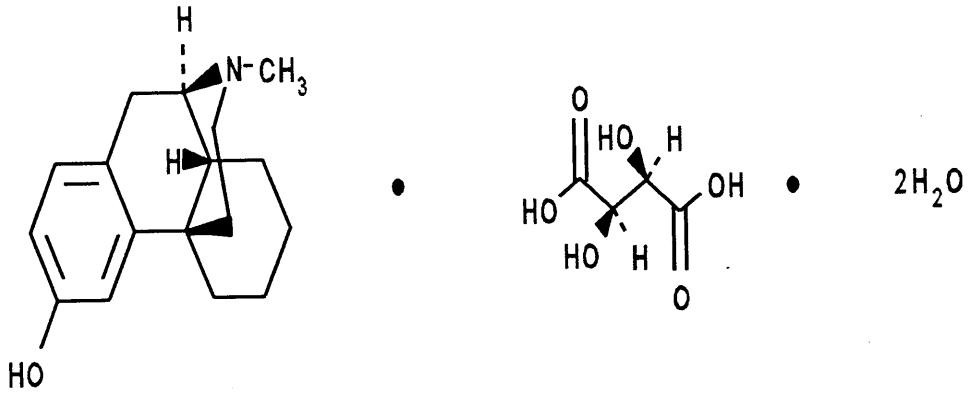
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF# [redacted]
DMF# [redacted]
DMF# [redacted]
DMF# [redacted]
DMF# [redacted]

13. DOSAGE FORM
Tablet

14. POTENCY
2 mg

15. CHEMICAL NAME AND STRUCTURE
17-Methylmorphinan-3-ol, tartrate (1:1) (salt) dihydrate.
$C_{17}H_{23}NO.C_4H_6O_6.2H_2O$ MW=443.49



STRUCTURAL FORMULA:
Levorphanol Tartrate USP

CHEMICAL FORMULA: $C_{17}H_{23}NO.C_4H_6O_6.2H_2O$; M.W. = 443.50
17-Methylmorphinan-3-ol, tartrate (1:1) (salt) dihydrate.
CAS [5985-38-6]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
The following deficiencies are noted in the review:
-Manufacturing and processing
-Laboratory controls
-Stability
-EER issued

18. CONCLUSIONS AND RECOMMENDATIONS
This application is considered as not approvable. The letter will be issued.

19. REVIEWER:
Sema Basaran Ph.D.

DATE COMPLETED:
10-16-97

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MINOR AMENDMENT

MAY 29 1998

ANDA 74-278

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Roxane Laboratories, Inc. PHONE: 800-848-0120

ATTN: Martin Williamson FAX: 614-276-0321

FROM: Timothy Ames PROJECT MANAGER (301) 827–5798

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated November 24, 1992, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levorphanol Tartrate Tablets USP, 2 mg.

Reference is also made to your amendment(s) dated December 19, 1997 and February 13, 1998..

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (____ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

CMC comments are attached

5/21/13

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1. CHEMIST'S REVIEW NO.4

2. ANDA # 74-278

3. NAME AND ADDRESS OF APPLICANT
Roxane Laboratories, Inc.
Attention: Sean Alan F.X. Reade
P.O. 16532
Columbus, OH 43216-6532

4. LEGAL BASIS FOR ANDA SUBMISSION
LevoDromoran Tablets - Hoffman- LaRoche
Exp. date: December 19, 1991. Levo-Dromoran has no pending patents or periods of exclusivity.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Levorphanol Tartrate
Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
November 24, 1992: Original submission.
June 16, 1995: amendment
April 29, 1997: Amendment
December 19, 1997: Facsimile amendment

FDA:
December 10, 1992: Acknowledgment letter.
June 2, 1993: Deficiency letter
December 21, 1995: Deficiency letter
November 28, 1997: Facsimile amendment

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF# [redacted]
DMF# [redacted]
DMF# [redacted]
DMF# [redacted]
DMF# [redacted]

13. DOSAGE FORM
Tablet

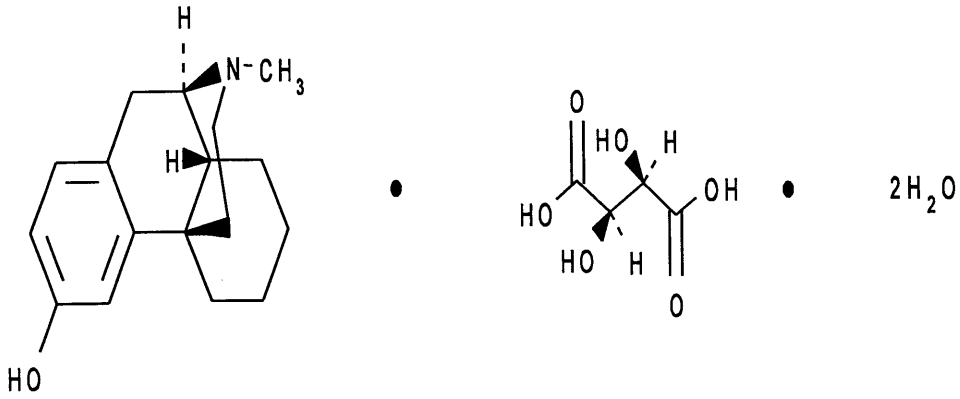
14. POTENCY
2 mg

[redacted]EARS THIS WAY
ON ORIGINAL

15. CHEMICAL NAME AND STRUCTURE

17-Methylmorphinan-3-ol, tartrate (1:1) (salt) dihydrate.

$C_{17}H_{23}NO.C_4H_6O_6.2H_2O$ MW=443.49



STRUCTURAL FORMULA:

Levorphanol Tartrate USP

CHEMICAL FORMULA: $C_{17}H_{23}NO.C_4H_6O_6.2H_2O$; M.W. = 443.50

17-Methylmorphinan-3-ol, tartrate (1:1) (salt) dihydrate.

CAS [5985-38-6]

16. RECORDS AND REPORTS

N/A

17. COMMENTS

The following deficiencies are noted in the review:

-Laboratory controls
-Stability
-EER issued

18. CONCLUSIONS AND RECOMMENDATIONS

This application is considered as not approvable. The letter will be issued.

19. REVIEWER: Sema Basaran Ph.D.

DATE COMPLETED: 1-5-98

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1. CHEMIST'S REVIEW NO.5

2. ANDA # 74-278

3. NAME AND ADDRESS OF APPLICANT
Roxane Laboratories, Inc.
Attention: Ann M. Maloney
P.O. 16532
Columbus, OH 43216

4. LEGAL BASIS FOR ANDA SUBMISSION
LevoDromoran Tablets - Hoffman- LaRoche
Exp. date: December 19, 1991. Levo-Dromoran has no pending patents or periods of exclusivity.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Levorphanol Tartrate Tablets USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
November 24, 1992: Original submission.
June 16, 1995: amendment
April 29, 1997: Amendment
December 19, 1997: Facsimile amendment
February 13, 1998: Telephone amendment
November 10, 1999: Telephone amendment

FDA:
December 10, 1992: Acknowledgment letter.
June 2, 1993: Deficiency letter
December 21, 1995: Deficiency letter
November 28, 1997: Facsimile amendment
January 7, 1998: Telephone conversation
February 23, 1998: Telephone conversation
May 29, 1999: Telephone deficiencies

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF# [redacted]
DMF# [redacted]
DMF# [redacted]
DMF# [redacted]
DMF# [redacted]
DMF# [redacted]
DMF# [redacted]
DMF# [redacted]

13. DOSAGE FORM
Tablet

14. POTENCY
2 mg

CHEMICAL NAME AND STRUCTURE:

LEVORPHANOL TARTRATE USP:

17-Methylmorphinan-3-ol, tartrate (1:1) (salt) dihydrate.
$C_{17}H_{23}NO.C_4H_6O_6.2H_2O$ MW=443.49

CHEMICAL FORMULA: $C_{17}H_{23}NO.C_4H_6O_6.2H_2O$; M.W. = 443.50
17-Methylmorphinan-3-ol, tartrate (1:1) (salt) dihydrate.
CAS [5985-38-6]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
The following are noted in the review:
-Labeling satisfactory on 10-22-97
-Bio. status- Acceptable on 10-9-97.
-CMC is acceptable on 11-24-99/2-16-00/2-23-00
-EER acceptable 2-22-00

18. CONCLUSIONS AND RECOMMENDATIONS
This application is considered approvable. The approval letter will be issued.

19. REVIEWER: Sema Basaran Ph.D.

DATE COMPLETED: 11-24-99/2-16-00/2-23-00

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-278

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 74-278 SPONSOR : Roxane Laboratories, Inc.
DRUG & DOSAGE FORM : Levorphanol Tartrate Tablet
STRENGTH : 2 mg
TYPE OF STUDY: Single-Dose Fasting
STUDY SITE: CLINICAL : [redacted]
ANALYTICAL : [redacted]

STUDY SUMMARY :

Parameter for **Total Levorphanol**	test Log LS mean	ref Log LS mean	ratio	90% CI (log).
Cmax(ng/mL)	16.67	16.89	0.99	(0.939; 1.037)
AUC(0-T) ngxhr/mL	183.36	189.36	0.98	(0.944; 1.027)
AUC(0-Inf)ngxhr/mL	190.45	193.82	0.98	(0.943; 1.024)
Tmax hr	2.06	1.87		
Half-life hr	10.37	10.22		

Parameter for **Free Levorphanol**	test Log LS mean	ref Log LS mean	ratio	90% CI (log).
Cmax(ng/mL)	2.93	3.30	0.89	(0.818; 0.966)
AUC(0-T) ngxhr/mL	36.15	37.84	0.96	(0.910; 1.002)
AUC(0-Inf)ngxhr/mL	38.71	40.44	0.96	(0.914; 1.003)
Tmax hr	2.10	2.15		
Half-life hr	10.63	11.10		

DISSOLUTION :

Conditions: Paddle apparatus, 50 rpm, 500 mL of water

Time(min)	Test Mean% (range)	Ref. Mean% (range)
10	87 ([redacted]	84 [redacted]
20	97 [redacted]	97 ([redacted]
30	99 [redacted]	97 [redacted]

Q = NLT ~ (Q) in 30 minutes (USP 23)

Lin-Whei Chuang
PRIMARY REVIEWER

BRANCH : 1

INITIAL : /S/ DATE : 9/26/97

Yih-Chain Huang, Ph.D.
TEAM LEADER

BRANCH : 1

INITIAL : /S/ DATE : 9/26/97

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL : /S/ DATE : 1/15/98

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL : _____ DATE : _____

APPEARS THIS WAY
ON ORIGINAL

OCT - 3 1997

Levorphanol Tartrate
Tablet, 2 mg
ANDA #74-278
Reviewer: L. Chuang

Roxane Laboratories, Inc.
Columbus, Ohio
Submission Date:
June 9, 1997
September 5, 1997

Review of an Amendment to a New In-Vivo Bioequivalence Study which was an Amendment to an Old Study

Background:

The bioequivalence study conducted by Roxane Laboratories, Inc. on its Levorphanol Tartrate tablet, 2 mg, lot #WA-R-17, as reported in the firm's submission of 11/24/92, was found unacceptable by the Division of Bioequivalence due to 6 deficiencies (see review of 02/02/93).

The firm then submitted the protocol and results of a new bioequivalence study titled "*A Pharmacokinetic Study to Assess the Bioequivalence of Levorphanol Tartrate 2 mg Tablets (Roxane, lot #950830) with Levo-Dromoran 2 mg tablets (Roche) Following Single Dose Administration, in Healthy Subjects Receiving Concomitant Doses of Naltrexone*" on 06/16/95 and 08/13/96, respectively. The results of this new study were found to be incomplete due to **4 deficiencies** (see review of 02/28/97). In the present submission, the firm responded to those deficiencies (on 06/09/97) and submitted the data diskette (on 09/05/97):

1. *In addition to total levorphanol, plasma samples should be assayed for free levorphanol as planned in the protocol.*

Firm's Response: After the telephone conversation with the Division of Bioequivalence on 04/01/97 (see attached memo), the firm analyzed the plasma samples, which had been in storage at -20° C since the clinical study during 06/30-7/12/95, for free levorphanol at the same analytical site , see review of 02/28/97) where the analysis of total levorphanol was conducted.

samples.

The stability of levorphanol after long term storage was studied using the QC samples which were prepared on 06/20/95 and stored under the same condition as study samples, -20°C, for 1 year and 9 months. The stability was found to be **80.8-82.0%** of the nominal values. When comparing to the results of analysis of same QC samples conducted on 06/23/95 (3 days after the preparation of the QC samples), the stability was found to be **84.9-90.4%.**

The specificity, limit of quantitation, recovery, and stability under various conditions, had all been validated previously (see review of 02/28/97).

The analytical method was further validated during the analysis of the study samples when 10 standard curves were conducted, each with duplicates of 3 levels of QC samples. The correlation coefficients were 0.9969 or larger. The precision was 2.73-9.80% CV for the standards and 4.88-10.61% CV for the QC samples. The accuracy was 95.50-102.35% for the standards and 98.00-103.73% for the QC samples.

Among the 936 plasma samples collected from the 26 subjects, 935 samples were analyzed. No re-assay was reported. The mean plasma concentration of free levorphanol at each sampling point after both treatments in 26 subjects and the mean pharmacokinetic parameters are presented below in Table 1.

Table 1: Mean (C.V.%) Plasma Free Levorphanol Concentrations (ng/mL) at Each Sampling Time Point (n = 26, dose = 2x2 mg)

Time (hour)	Roxane (Treatment A)	Roche (Treatment B)
0	0	0
0.50	1.30 (48)	1.52 (50)
1.00	2.51 (36)	2.68 (39)
1.50	2.69 (31)	2.96 (28)
2.00	2.76 (30)	2.98 (26)
2.50	2.75 (27)	2.89 (26)
3.00	2.64 (27)	2.81 (27)
4.00	2.44 (23)	2.56 (26)
5.00	2.19 (23)	2.41 (40)
6.00	2.01 (26)	2.33 (54)
8.00	1.59 (25)	1.58 (33)
10.00	1.29 (22)	1.32 (30)
12.00	1.04 (22)	1.10 (31)

16.00	0.78 (26)	0.84 (31)
24.00	0.51 (26)	0.53 (40)
36.00	0.24 (32)	0.25 (42)
48.00	0.11 (73)	0.10 (98)
72.00	0	0
AUC_{0-t} (ng*hr/mL)	37.40 (23)	39.85 (30)
AUC_{0-inf} (ng*hr/mL)	40.46 (12)	42.67 (29)
C_{max} (ng/mL)	3.04 (27)	3.50 (37)
$LNAUC_{0-t}$	3.597 (36.49[a])	3.643 (38.21[a])
$LNAUC_{0-inf}$	3.678 (39.57[a])	3.713 (40.98[a])
LNC_{max}	1.075 (2.930[a])	1.193 (3.30[a])
T_{max} (hour)	2.06 (46)	2.15 (56)
$T_{1/2}$ (hour)	12.50 (20)	11.93 (24)

a = geometric mean

All pharmacokinetic parameters were analyzed by Analysis of Variance with sequence, subject (sequence), period and treatment as factors. The analyses of variance included calculations of least squares means and estimated differences between the two formulations.

There were significant differences (p=0.02-0.04) between the two treatments for C_{max}, AUC_{0-t}, and LNC_{max} and very significant differences (p=0.0001) between periods for AUC_{0-t}, AUC_{0-inf}, $LNAUC_{0-t}$, and $LNAUC_{0-inf}$. The LS means of AUC_{0-t}, AUC_{0-inf}, C_{max}, $LNAUC_{0-t}$, $LNAUC_{0-inf}$ and LNC_{max}, ratio of these means and the 90% confidence interval of test product versus the reference product are presented in Table 2.

Table 2: Statistical Analysis of Free Levorphanol -- 2x2 mg -- (n=26)

Parameter	LS Means (Test - Roxane)	LS Means (Reference - Roche)	T/R	90% Confidence Interval
AUC_{0-t}	37.40	39.85	0.94	(0.878; 0.999)
$LNAUC_{0-t}$	3.59598 (36.49[a])	3.64271 (38.19[a])	0.95[b]	(0.901; 1.013)
AUC_{0-inf}	40.46	42.67	0.95	(0.890; 1.007)
$LNAUC_{0-inf}$	3.67796 (39.56[a])	3.71326 (40.99[a])	0.96[b]	(0.914; 1.020)

C_{max}	3.04	3.50	0.87	(0.749; 0.990)
LNC_{max}	1.07505 (2.93[a])	1.19265 (3.30[a])	0.89[b]	(0.805; 0.982)

a = Least Square Geometric Mean b = Ratio of Least Square Geometric Means

Reviewer's Comments:

a. The long-term stability of study samples are acceptable as evident from the stability of the QC samples prepared 10 days before the clinical study was conducted.

b. Two sample values (out of 936 study samples) were reported as missing, i.e. subject #2, 6-hour, treatment B and subject #11, 10-hour, treatment A. These missing values should not affect the outcome of the study since the T_{max} in both cases were 2.5 hours.

c. Using the plasma concentration data submitted by the firm on the data diskette, the LS means and the 90% confidence intervals were re-calculated and presented below in Table 3.

Table 3: Statistical Re-Analysis of Free Levorphanol -- 2x2 mg -- (n=26)

Parameter	LS Means (Test - Roxane)	LS Means (Reference - Roche)	T/R	90% Confidence Interval
AUC_{0-t}	37.18	39.56	0.94	(0.889; 0.991)
$LNAUC_{0-t}$	36.15[a]	37.84[a]	0.96[b]	(0.910; 1.002)
AUC_{0-inf}	39.74	42.18	0.94	(0.893; 0/991)
$LNAUC_{0-inf}$	38.71[a]	40.44[a]	0.96[b]	(0.914; 1.003)
C_{max}	3.04	3.50	0.87	(0.769; 0.969)
LNC_{max}	2.93[a]	3.30[a]	0.89[b]	(0.818; 0.966)

a = Least Square Geometric Mean b = Ratio of Least Square Geometric Means

d. The 90% confidence intervals calculated by the reviewer differ only slightly from those submitted by the firm. However, both sets of confidence intervals for LNC_{max}, $LNAUC_{0-t}$, and $LNAUC_{0-inf}$, either submitted by the firm or calculated by the review, are within the 80-125% limits.

e. The T_{max} of subject #14 during treatment A was 0.5 hour which was the first blood sampling time point. The C_{max} thus estimated might not be accurate. However, after the deletion of data of subject #14, the 90% confidence intervals for LNC_{max}, $LNAUC_{0-t}$, and $LNAUC_{0-inf}$ are still within the 80-125% limits.

2. Data diskette containing information of all plasma concentrations of each analyte and the pharmacokinetic parameters of each subject should be submitted.

Firm's Response: The firm submitted the requested information and the re-calculation was conducted and presented below in Table 4:

Table 4: Statistical Re-Analysis of Total Levorphanol – 2x2 mg – (n=26)

Parameter	LS Means (Test - Roxane)	LS Means (Reference - Roche)	T/R	90% Confidence Interval
AUC_{0-t}	190.93	192.06	0.99	(0.950; 1.029)
$LNAUC_{0-t}$	186.36[a]	189.36[a]	0.98[b]	(0.944; 1.027)
AUC_{0-inf}	193.96	196.59	0.99	(0.949; 1.025)
$LNAUC_{0-inf}$	190.45[a]	193.82[a]	0.98[b]	(0.943; 1.024)
C_{max}	17.14	17.18	1.00	(0.951; 1.044)
LNC_{max}	16.67[a]	16.89[a]	0.99[b]	(0.939; 1.037)

a = Least Square Geometric Mean b = Ratio of Least Square Geometric Means

Reviewer's Comment: The 90% confidence intervals calculated by the reviewer differ only slightly from those submitted by the firm. However, both sets of confidence intervals for LNC_{max}, $LNAUC_{0-t}$, and $LNAUC_{0-inf}$, either submitted by the firm or calculated by the review, are within the 80-125% limits.

3. Evidence demonstrating the lack of cross-reactivity in the assay method between levorphanol and naltrexone (or its 6-β-naltrexol metabolite) should be submitted.

A solution of naltrexone (100 ug/mL) was injected into the [redacted] and no quantifiable peaks at the retention time for levorphanol were observed.

4. The clinical records, medical records/case reports of study subjects should be submitted.

The records and reports were submitted.

Overall Comment:

The results for both the free and total levorphanol are acceptable. The dissolution data submitted previously (06/16/95) comply with the specification of USP 23.

Recommendation:

1. The fasting bioequivalence study conducted by Roxane Laboratories, Inc. on its levorphanol tartrate 2 mg tablet, Lot #950830, comparing to Levo-Dromoran^{R} 2 mg tablet, lot #1068 manufactured by Roche Laboratories, has been found acceptable by the Division of Bioequivalence. The study demonstrated that Roxane's levorphanol tartrate 2 mg tablet is bioequivalent to the reference product, Levo-Dromoran^{R} 2 mg tablet manufactured by Roche Laboratories, when administered under fasting condition.

2. The dissolution testing conducted by Roxane Laboratories, Inc. on its levorphanol tartrate 2 mg tablet, Lot #950830, comparing to Levo-Dromoran^{R} 2 mg tablet, lot #1068 manufactured by Roche Laboratories, has been found acceptable by the Division of Bioequivalence. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test products should meet the following specification recommended by the USP 23:

   Not less than — (Q) of the labeled amount of levorphanol tartrate in the dosage form is dissolved in 30 minutes.

/S/ 9/26/97

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG

/S/ 9/26/97

Concur: /S/ Date: 10/3/97

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA 74-278 (original, duplicate), Chuang, HFD-652 (Huang), Drug File, Division File.

First Draft 09/25/97, LWC, C:\wpfiles\74-278sd.697
Final Pink 09/26/97, LWC, x:\new\firmsnz\roxane\ltrs&rev\74278a.697

FEB 28 1997

Levorphanol Tartrate
Tablet, 2 mg
ANDA #74-278
Reviewer: L. Chuang

Roxane Laboratories, Inc.
Columbus, Ohio
Submission Date:
August 13, 1996

Review of a New In-Vivo Bioequivalence Study and Dissolution Data:
(Amendment to an Old Study)

Background:

The original submission on 11/24/92 included an *in vivo* bioequivalence study which was found to be unacceptable.

In this current submission, the firm reported the results of another bioequivalence study titled "A Pharmacokinetic Study to Assess the Bioequivalence of Levorphanol Tartrate 2 mg Tablets (Roxane) with Levo-Dromoran 2 mg tablets (Roche) Following Single Dose Administration, in Healthy Subjects Receiving Concomitant Doses of Naltrexone" which differed from the previous study in two major aspects:

1. Study subjects received concomitant doses of naltrexone in the new study. Naltrexone is an antagonist competing for the same receptor sites as morphine (or levorphanol) and is expected to diminish the potential adverse effects of levorphanol, especially respiratory depression. It has been reported that the use of a twice a day oral dose of 50 mg of naltrexone slightly alter the absolute bioavialability of oral morphine, but do not interfere with the determination of comparative bioavailability.

2. The analytical method used in the new study was [redacted] instead the [redacted] method used in the old study.

Bioequivalence Study -- 2x2 mg -- in Subjects Receiving Concomitant Doses of Naltrexone

The objective of this study was to assess the bioequivalence of two formulations of levorphanol tartrate when administered as a single 4 mg oral dose - 2 x 2 mg levorphanol tartrate tablets (Roxane), compared with 2 x 2 mg Levo-Dromoran^{R} tablets (Roche) - in healthy male subject. Doses of naltrexone (100 mg/day) were given concomitantly at 24 hours prior, 0.5 hour prior and 24 hours after the levorphanol dose.

The clinical portion of the study was conducted during 06/30-07/12/95 at [redacted]
in [redacted]

The analytical portion of the study was conducted at the [redacted]

[redacted] during 07/18-08/02/95 (study samples were received during 07/5-12/95) with [redacted] as the principal scientist.

The design is a single-dose, 2-period, 2-treatment crossover of the test product and the reference product in fasted subjects.. The protocol was reviewed and approved by the [redacted] Review Board on June 13, 1995.

Twenty-six (24+2) men (22 Caucasians, 2 Hispanics, 1 Black and 1 American Indian) who were 19-52 years old, weighed within ±15% of the ideal weight for their height and frame size were enrolled. Eleven (11) of them were non-smokers. Subjects #25 & 26 were recruited in case any subject from #1-24 dropped out.

Screening of subjects were conducted within 14 days prior to study enrollment. Subjects' medical history, results from physical examination and clinical laboratory tests were assessed by the PI. The inclusion criteria were:

1. Males 19-55 years of age with body weight within 15% of the ideal weight for their height and frame.
2. No clinically significant abnormal findings in physical examination, medical history, and laboratory tests.
3. Negative urine screen for alcohol and drugs of abuse.
4. Consent to participate in this study.

The exclusion criteria were:

1. Known allergy to naltrexone, levorphanol tartrate or products containing codeine, morphine, hydromorphone, hydrocodone, or oxycodone.
2. Participation in a clinical trial, blood donation of one pint or more, abnormal diet, or treatment with any enzyme altering agents, within 30 days prior to study initiation.
3. Plasmapheresis within 7 days prior to study initiation.
4. Use of any prescription medication 14 days prior to study initiation.
5. Use of any OTC medication 72 hours prior to study initiation.

Twenty-six (26) qualified subjects were instructed not to consume any alcoholic beverage for 48 hours prior to or during each study period. At check-in time on day -2, they completed a brief questionnaire to affirm the compliance of the exclusion criteria, provided a urine sample for alcohol and drug of abuse screen, and signed the informed consent forms.

Subjects received naltrexone tablets (2 x 50 mg) at -24 hours, -0.5 hour and 24 hours after one of the following treatments randomly assigned on 07/02/95 and switched over to the alternative treatment on 07/09/95:

Treatment A - Test Drug: Levorphanol Tartrate tablet, 2 X 2 mg, Roxane Laboratories,

lot #950830, potency 100.6%, lot size [redacted] tablets.

Treatment B - Reference Drug: Levo-Dromoran[R] tablet, 2 X 2 mg, Roche Laboratories, lot #1068, potency 100.6% expires 1/1/98.

Each treatment was taken with 240 mL of water. Blood samples (14 mL each) were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours after dose. The washout period between the two treatments was 7 days. Plasma samples were stored at -20°C until analyzed during the time period of 07/18-08/02/95.

For safety assessment, respiration and pulse rates were recorded and level of consciousness was noted at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 and 48 hours post-dose. Subjects remained in the clinical facility until the 48 hours post-dose blood collection. The were required to return to the clinic for the 72-hour blood collection. At the completion of the study, vital signs, physical examination and clinical laboratory tests were evaluated before subjects were released.

Analytical Method:

[redacted]

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It was mentioned briefly in the report that none of the subjects had any medically abnormal findings at the prestudy screening or the poststudy evaluation. **However, no clinical records, medical records/case reports were submitted.**

Among the 936 plasma samples collected from the 26 subjects, 3 were re-assayed because the original results were incongruous to pharmacokinetic profile. The mean of the duplicate reassays was reported. The mean plasma concentration of total levorphanol at each sampling point after both treatments in 26 subjects and the mean pharmacokinetic parameters are presented below in Table 2.

Table 2: Mean (C.V.%) Plasma Total Levorphanol Concentrations (ng/mL) at Each Sampling Time Point (n = 26, dose = 2x2 mg)

Time (hour)	Roxane (Treatment A)	Roche (Treatment B)
0	0	0
0.50	5.39 (56)	5.76 (40)
1.00	13.29 (35)	13.63 (23)
1.50	15.38 (32)	16.42 (20)
2.00	15.88 (26)	16.11 (19)
2.50	15.04 (24)	15.49 (20)
3.00	13.89 (21)	14.40 (18)
4.00	12.23 (23)	12.37 (20)
5.00	10.30 (19)	10.11 (23)
6.00	9.48 (23)	9.28 (22)
8.00	7.51 (25)	7.49 (22)
10.00	6.21 (22)	6.34 (23)
12.00	5.09 (21)	5.26 (21)
16.00	3.87 (21)	3.83 (23)
24.00	2.13 (32)	2.19 (31)
36.00	1.11 (34)	1.10 (45)
48.00	0.53 (39)	0.55 (57)
72.00	0.14 (83)	0.14 (110)
AUC_{0-t} (ng*hr/mL)	191.43 (20)	193.94 (18)
AUC_{0-inf} (ng*hr/mL)	196.05 (19)	199.47 (18)
C_{max} (ng/mL)	17.14 (23)	17.18 (18)

$LNAUC_{0-t}$	187.92[a]	191.33[a]
$LNAUC_{0-inf}$	192.67[a]	196.76[a]
LNC_{max}	16.68[a]	16.89[a]
T_{max} (hour)	2.06 (46)	1.85 (28)
$T_{1/2}$ (hour)	12.50 (20)	12.32 (30)

a = geometric mean

All pharmacokinetic parameters were analyzed by Analysis of Variance with sequence, subject (sequence), period and treatment as factors. The analyses of variance included calculations of least squares means and estimated differences between the two formulations.

There were significant difference (p=0.0003-0.0006) between the two periods for AUC_{0-t}, AUC_{0-inf}, $LNAUC_{0-t}$, and $LNAUC_{0-inf}$. The LS means of AUC_{0-t}, AUC_{0-inf}, C_{max}, $LNAUC_{0-t}$, $LNAUC_{0-inf}$ and LNC_{max}, ratio of these means and the 90% confidence interval of test product versus the reference product are presented in Table 3.

Table 3: Statistical Analysis of Total Levorphanol -- 2x2 mg -- (n=26)

Parameter	LS Means (Test - Roxane)	LS Means (Reference - Roche)	T/R	90% Confidence Interval
AUC_{0-t}	191.43	191.94	1.00	(0.949; 1.025)
$LNAUC_{0-t}$	5.23614 (187.94[a])	5.25354 (191.24[a])	0.98[b]	(0.944; 1.024)
AUC_{0-inf}	196.05	199.47	0.98	(0.946; 1.020)
$LNAUC_{0-inf}$	5.26098 (192.67[a])	5.28202 (196.77[a])	0.98[b]	(0.940; 1.020)
C_{max}	17.14	17.18	1.00	(0.951; 1.044)
LNC_{max}	2.81364 (16.67[a])	2.82686 (16.89[a])	0.99[b]	(0.939; 1.037)

a = Least Square Geometric Mean
b = Ratio of Least Square Geometric Means

Comments on the Bioequivalence Study:

1. The plasma samples were not assayed for free levorphanol as planned in the protocol.

2. The data diskette containing results of total levorphanol shown in Tables 2&3 has not been submitted.

3. The lack of cross-reactivity in the assay method between levorphanol and naltrexone (or its 6-β-naltrexol metabolite) had not been demonstrated as indicated in the protocol.

4. The clinical records, medical records/case reports were not submitted

Dissolution Testing:

The comparative dissolution profile of the test and reference products are presented below in Table 4:

Table 4 - In Vitro Dissolution Testing

Drug (Generic Name): Levorphanol Tartrate
Dosage Form: Tablet
Dose Strength: 2 mg
ANDA No.: 74-278
Firm: Roxane Laboratories, Inc.
Submission Date: 08/13/96

I. Conditions for Dissolution Testing:

USP XXIII Apparatus: Paddle RPM: 50
No. Units Tested: 12
Medium: Water Volume: 500 mL
Tolerance: NLT — Q) of the labeled amount is dissolved in 30 minutes
Reference Drug: Levo-Dromoran[R] (Roche Laboratories)
Assay Methodology: —

II. Results of In Vitro Dissolution Testing:

Sampling Times (minute)	Test Product Lot # 950830 Strength (mg): 2			Reference Product Lot # 1068 Strength (mg): 2		
	Mean %	Range	%CV	Mean %	Range	%CV
10	87	—	14.4	84	—	6.1
20	97	—	7.5	97	—	5.2
30	99	—	5.9	97	—	6.2

Comment on the Dissolution Testing:

The results of dissolution testing are in compliance with USP dissolution specification of "not less than — in 30 minutes" with the USP 23 paddle method at 50 rpm in 500 mL of water.

Deficiencies:

1. In addition to total levorphanol, plasma samples should be assayed for free levorphanol as planned in the protocol.

2. A data diskette containing information of all plasma concentrations of each analyte and the pharmacokinetic parameters of each subject should be submitted.

3. Evidence demonstrating the lack of cross-reactivity in the assay method between levorphanol and naltrexone (or its 6-β-naltrexol metabolite) should be submitted.

4. The clinical records, medical records/case reports of study subjects should be submitted.

Recommendation:

The bioequivalence study conducted by Roxane Laboratories, Inc. on its Levorphanol tartrate tablet, 2 mg, lot #950830, has been found incomplete by the Division of Bioequivalence due to deficiencies 1-4.

The deficiencies and recommendation should be forwarded to the firm.

/S/ 2/26/97

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG /S/ 2/26/97
FT INITIALED YCHUANG /S/

Concur: _____ Date: 2/28/97
Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA 74-278 (original, duplicate), Chuang, HFD-652 (Huang), Drug File, Division File.

Firsr Draft 02/21/97, LWC, C:\wpfiles\74-278sd.896
Final Pink 02/25/97, LWC, x:\new\firmsnz\searle\ltrs&rev\74-278sd.896

OCT 26 1995

Levorphanol Tartrate
Tablet, 2 mg
ANDA #74-278
Reviewer: L. Chuang

Roxane Laboratories, Inc.
Columbus, Ohio
Submission Date:
June 16, 1995

Review of a Major Amendment

The bioequivalence study conducted by Roxane Laboratories, Inc. on its Levorphanol Tartrate tablet, 2 mg, lot #WA-R-17, as reported in the firm's submission of 11/24/92, was found unacceptable by the Division of Bioequivalence due to the 6 deficiencies stated in the previous review of 02/02/93.

In the present submission, the firm presented a new protocol for a new bioequivalence study and stated that the study was to begin on **July 1, 1995.** Therefore, the study has already initiated and the protocol does not need to be reviewed at present.

The firm also submitted the dissolution data of new lots of test and reference drugs. The method and result are presented below:

In Vitro Dissolution Testing

Drug (Generic Name): Levorphanol Tartrate

Dose Strength: 2 mg
ANDA No.: 74-278
Firm: Roxane Laboratories, Inc.
Submission Date: 6/16/95

I. Conditions for Dissolution Testing:

USP XXIII Apparatus: Paddle RPM: 50
No. Units Tested: 12
Medium: Water Volume: 500 ml
Tolerance: NLT — of Levorphanol(Q) in 30 minutes
Reference Drug: Levor-Dromoran^{R} Tablet (Roche)
Assay Methodology: [illegible]

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 950830 Strength (mg): 2			Reference Product Lot # 1068 Strength (mg): 2		
	Mean % dissolved	Range	%CV	Mean % dissolved	Range	%CV
10	87	[illegible]	6.1	84	[illegible]	6.1
20	97	[illegible]	5.2	97	[illegible]	5.2
30	99	[illegible]	5.9	97	[illegible]	6.2

Comment:

The above dissolution results comply with the USP 23 specification of "not less than — (Q) of levorphanol is dissolved in 30 minutes for levorphanol tartrate tablet.

Recommendation:

1. No recommendation is made at present for the protocol of the bioequivalence study since the study has already begun.

2. The dissolution testing conducted by Roxane Laboratories, Inc. on its Levorphanol Tartrate Tablet, 2 mg, Lot #950830, is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water at 37° C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than — of the labeled amount of levorphanol is dissolved in 30 minutes.

/S/

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

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FT INITIALED YHUANG

/S/ 10/26/95

Concur: /S/ Date: 10/26/95
for Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 74-278 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-652 (Huang, Chuang), Drug File, Division File.

LWC/102695/dbm/WP #74278AM.695

FEB 2 1993

Levorphanol Tartrate
Tablet, 2 mg
ANDA #74-278
Reviewer: L. Chuang
WP #74278SD.N92

Roxane Laboratories, Inc.
Columbus, Ohio
Submission Date:
November 24, 1992

Review of an In-Vivo Bioequivalence Study and Dissolution Data

Introduction:

Levorphanol is a potent synthetic analgesic related chemically and pharmacologically to morphine. It produces stronger and longer lasting analgesia than either meperidine or morphine.

The pharmacokinetics of levorphanol have been studied in a limited number of cancer patients. Following IV administration plasma levels of levorphanol decline in a triexponential manner with a terminal half-life of 11-16 hours. Levorphanol is well absorbed after oral administration with peak blood occurring 1 hour after dosing. It is extensively metabolized in the liver and is eliminated as the glucuronide metabolite.

Levorphanol tartrate is commercially available as Levo-Dromoran injection, 2 mg/mL, and Levo-Dromoran oral tablet, 2 mg, both manufactured by Hoffmann la Roche Inc.. The average adult dose is 2 mg orally or subcutaneously. It is a Schedule II drug under Controlled Substance Act.

Bioequivalence Study:

The objective of this study was to evaluate the relative bioavailability of levorphanol tartrate tablets (2 mg, Roxane) and Levo-Dromoran (2 mg, Roche).

The clinical portion of the study was conducted during November 17-20 and 24-27, 1986 at _____ in _____, _____. as the principle investigator.

The analytical portion of the study was conducted at the _____ during 12/08/86 to 01/14/87 with _____ as the associate director.

The design is a single-dose, 2-period, 2-treatment crossover of the test product and the reference product. The protocol was reviewed and approved by the _____ Review Board on October 28, 1986.

Twenty-six (26) men with 20-51 years of age, weighed within ±15% of the ideal weight for their height and frame size were enrolled.

They were given a physical examination on November 11, 1986. Volunteers selected for the study had no clinically significant abnormal findings. Subjects with a history of chronic alcoholic consumption, drug addiction, GI, renal, hepatic or cardiovascular disease, tuberculosis, epilepsy, asthma, diabetes, psychosis or glaucoma and subjects who had allergic response to levorphanol or other opioids were excluded from the study. Subjects #25 & 26 were recruited in case any subject from #1-24 dropped out.

All 26 subjects were instructed not to take any medications for two weeks prior to and during the study period and read and signed an Informed Consent Form prior to study initiation. They were fasted for 9 hours before and 4 hours after subjecting to one of the following randomly assigned drug treatments on November 18 and 25, 1992:

Treatment A - Test Drug: Levorphanol Tartrate tablet, 2 X 2 mg, Roxane batch #Wa-R-17, potency 96.6%, lot size not given.

Treatment B - Reference Drug: Levo-Dromoran^{R} tablet, 2 X 2 mg, Roche lot #1026, potency 97.9% expiration date not given.

Each treatment was taken with 180 mL of water. Blood samples (10 mL each) were collected into heparinized tubes at 0, 0.5, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours after dose. The washout period between the two treatments was 7 days.

Subject #26 did not report for study initiation and was dropped from the study. Subject #19 was removed from the study on 11/26/86 by Dr. Kisicki because of the inability to obtain sufficient blood samples from his vein. Consequently, among the 24 subjects who completed the study, 13 had treatment A during phase 1 and treatment B during period 2; and vice versa was true for the remaining 11 subjects.

Out of the 24 subjects who completed the study, 19 reported adverse effects. The most common symptom was vomiting; 13 subjects vomited, 10 after both treatments, 1 after treatment A and 2 after treatment B. The other adverse effects included fainting, headache, dizzy, hearing impairment, itching, nausea and hot flashes. These adverse effects occurred about equally after treatment A and treatment B.

Analytical Method:

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Stability was not evaluated, but the storage period between the completion of clinical study and the beginning of analytical process was only 10 days.

Results:

Among the 720 samples collected from the 24 subjects, 29 were reassayed because the original results were incongruous to pharmacokinetic profile and 6 were reassyed because the original concentrations were above quantifiable limit. However, there were no raw data of the reassay results and the firm did not include any explanation of the final results reported for these reassayed samples.

The mean plasma concentrations of free and total levorphanol at each sampling point after both treatments in 24 subjects and the mean pharmacokinetic parameters are presented below in Tables 1&2.

Table 1

Mean (C.V.%) Plasma Free Levorphanol Concentrations (ng/ml) at Each Sampling Time Point (n = 24)

Time (hours)	Roxane (Treatment A)		Roche (Treatment B)	
0	0		0	
0.50	0.49	(110)	0.54	(104)
0.75	1.15	(69)	1.27	(54)
1.00	1.83	(47)	1.92	(47)
1.25	2.28	(30)	2.33	(36)
1.50	2.58	(27)	2.53	(34)
2.00	2.71	(23)	2.83	(27)
3.00	2.67	(22)	2.75	(22)
4.00	2.48	(22)	2.56	(24)
6.00	1.85	(23)	1.96	(25)
8.00	1.55	(20)	1.62	(25)
12.00	0.99	(31)	1.05	(31)
16.00	0.75	(47)	0.79	(43)
24.00	0.35	(117)	0.29	(134)
36.00	0.03	(533)	0.03	(467)
48.00	0.03	(467)	0	
AUC_{0-t}	28.65	(35)	28.66	(33)
AUC_{0-inf}	38.80	(38)	38.19	(30)
C_{max} (ng/mL)	2.88	(21)	2.98	(23)
T_{max} (hr)	2.33	(47)	2.18	(30)
$T_{1/2}$ (hr)	9.13	(55)	8.42	(31)

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Table 2

Mean (C.V.%) Plasma Total Levorphanol Concentrations (ng/ml) at Each Sampling Time Point (n = 24)

Time (hours)	Roxane (Treatment A)		Roche (Treatment B)	
0	0.07	(300)	0.04	(425)
0.50	2.29	(74)	2.40	(64)
0.75	4.48	(46)	4.33	(46)
1.00	6.20	(32)	6.31	(36)
1.25	7.64	(19)	7.61	(30)
1.50	8.37	(17)	8.27	(30)
2.00	8.82	(17)	8.88	(20)
3.00	8.25	(18)	8.57	(16)
4.00	7.65	(18)	7.93	(16)
6.00	6.10	(18)	6.31	(19)
8.00	4.68	(22)	5.04	(21)
12.00	3.79	(19)	3.90	(21)
16.00	2.92	(20)	2.99	(25)
24.00	1.76	(22)	1.81	(24)
36.00	1.11	(28)	1.09	(27)
48.00	0.48	(94)	0.54	(81)
AUC_{0-t}	125.19	(18)	128.99	(24)
C_{max} (ng/mL)	8.94	(16)	9.40	(15)
T_{max} (hr)	1.83	(22)	2.07	(32)

All pharmacokinetic parameters were analyzed by Analysis of Variance with sequence, subject (sequence), period and treatment as factors. The analyses of variance included calculations of least squares means and estimated differences between the two formulations.

There were no significant differences ($p<0.05$) between the two drug treatments, two sequences or two periods for each parameter of the free and total levorphanol except that the C_{max} of total levorphanol was significantly higher for the reference product than the test product. The LS means of AUC_{0-t}, AUC_{0-inf} and C_{max}, ratio of these means and the 90% confidence interval of test product versus the reference product are presented in Tables 3&4.

Dissolution Testing:

The firm conducted dissolution testing on its Levorphanol Tartrate Tablet, 2 mg, lot #Wa-R-17, compared to the reference product, Levo-Dromoran[R] Tablet, 2 mg, lot #1059. The method used and results are presented in Table 5.

Table 5. In-Vitro Dissolution Testing

I. **Conditions for Dissolution Testing:**

USP XXII Basket ___ **Paddle** xx **RPM** 50 **No. Units Tested:** 12
Medium: Water
Reference Drug: (Manuf.) Levo-Dromoran (Roche)
Assay Methodology: ~~~~~~~~~~

II. **Results of In-Vitro Dissolution Testing:**

Sampling Times (min)	Test Product			Reference Product		
	Mean % Dissolved	Range	(%CV)	Mean % Dissolved	Range	(%CV)
	Lot # Wa-R-17 Strength: 2 mg			Lot #1059 Strength: 2 mg		
10	103	~~~~	(8.7)	108	~~~~	(5.6)
20	109	~~~~	(3.7)	112	~~~~	(2.5)
30	112	~~~~	(2.0)	116	~~~~	(5.2)

Comments on the Dissolution Testing:

1. The results of dissolution testing are in compliance with USP dissolution specification of "not less than ~~ in 30 minutes" with the USP XXII paddle method at 50 rpm in 500 mL of water.

2. The reference product used in the above dissolution testing was a different lot (lot #1059) than the lot used in the bioequivalence study (lot #1026).

Formulation:

Each white to mottled off-white flat tablet with beveled edges contains:

ingredient	per tablet
Levorphanol Tartrate	2.04 mg
Lactose NF (Anhydrous)	[illegible]
Starch NF	[illegible]
Stearic Acid NF	[illegible]
Talc USP	[illegible]
Magnesium Stearate NF	[illegible]
Total	100 .00 mg

Deficiencies:

1. The limit of quantitation of [illegible] as defined by the firm had not been validated since only the concentration range of [illegible] were validated with reliable accuracy and recision.

2. The specificity of the [illegible] was not confirmed by testing for possible interference from other structurally related substances in the plasma.

3. The firm is advised to employ an analytical method which would enable the accurate measurement of levorphanol at low concentration and the computation of AUC_{0-t} and estimation of AUC_{0-inf} should always result in the ratio of AUC_{0-t}/AUC_{0-inf} >0.80.

4. The firm should be advised to provide information on the procedures of any reassays and justification for the values presented in the final report for these repeated samples.

5. A comparative dissolution testing should be performed on the same lot of test and reference product used in the bioequivalence study.

6. The firm should assure that the lot size of the test product lot used in any bioequivalence study is at least [illegible] dose units.

Recommendation:

The bioequivalence study conducted by Roxane Laboratories, Inc. on its Levorphanol tartrate tablet, 2 mg, lot #WA-R-17, has been found unacceptable by the Division of Bioequivalence due to reasons cited in the comments and deficiencies sections.

The comments, deficiencies and recommendation should be forwarded to the firm.

/S/

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

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Concur: _____ Date: 6/2.93

Agnes Wu, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA 74-278 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-652 (Wu, Chuang), Drug File, Division File.

LC/012593/ntp/012793/WP #74278SD.N92

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-278

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 74-278 DRUG PRODUCT: Levorphanol Tartrate Tablets USP

FIRM: Roxane Laboratories, Inc. DOSAGE FORM: Tablet

STRENGTH: 2 mg

CGMP STATEMENT/EIR UPDATE STATUS:
CGMP certification is satisfactory (See Page 123).
EIR update : EER acceptable on 2-22-2000.

BIO STUDY: Satisfactory.
Acceptable for 2mg tablets, lot# 950830; Lin-Whei Chuang, October 26, 1997.

Dissolution specifications recommended by DOB (per USP):

NLT [redacted](Q) dissolved in 30 minutes.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Not required, USP product.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:
Containers used in the stability testing are the same as described in the container section.

Container for 100's:

Bottle : [redacted] 150 cc Square white
Resin: [redacted]
Manufacturer: [redacted]

Closure for 100's:

[redacted] CRC cap with [redacted] and [redacted] CRC cap with

Stability protcol acceptable; expiration date of 24 months based on satisfactory stability data.

LABELING:
Satisfactory per A.Vezza on 10-22-97.

STERILIZATION VALIDATION (IF APPLICABLE):

ZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Levorphanol Tartrate Tablets , 2 mg, batch # 950830 used for bio study;
The size of the bio batch was [redacted] tablets.
Firm's [redacted] OK: Yes [redacted]
DMF# [redacted] .

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

Stability for biobatch, lot# 950830, batch size [redacted] tablets;
lot# 961429, [redacted] tablets; 150 cc Square Bottle with neck ring and [redacted] stability data submitted in 4/29/97.
Lot# 991458 2 mg Tablets [redacted] Tablets; 150 cc Square Bottle with neck ring and [redacted] and cotton and desiccant;
stability data submitted in 11/10/99.

Different batch prepared due to new container/closure system but manufactured via the same process. Stability data is satisfactory to support 24 months tentative expiration.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

For 2 mg Tablets: [redacted] Tablets

Manufacturing process is the same as bio and stability batches. Scale-meets OGD PPG 22-90.

CHEMIST: S. Basaran /S/ DATE:2-23-2000 3/13/2000

Team Leader: U. V. Venkataram /S/ DATE:2-24-2000

3-13-2000.

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ON ORIGINAL

4/1/97 Lizzie Sanchez
Lin Chuang

ANDA 74-278/Levorphanol Tablets 2 mg
Roxane Laboratories
Sue Bastaja
Beverly Wenn, Medical Department
Anne Walzillig, Product Development
Elizabeth Ernst, Medical Dept

APPEARS THIS WAY ON ORIGINAL

Did Roxane measure free levorphanol? No, they did not measure free levorphanol levels. Samples are frozen, degradation unknown. The samples are 2 years old. The firm was asked to check a few samples for degradation. If there was no degradation, they should provide as many subjects' free levorphanol levels as possible.

The firm argued the fact that a letter dated June 30, 1995 was sent to them from Dr. Keith Chan, previous Division Director, stating that only total levorphanol levels were required to establish bioequivalence. However, aften an internal meeting 3/25/97, between Nick Fleischer (new Director) and Yi Huang (Team Leader), it was determined that a misunderstanding might have occurred when that letter was sent asking only for total levorphanol levels. It is the reviewer's position (Chuang) that free levels should be required as evidence of bioequivalence. This position was shared by both TeamLeader and Director.

The firm agreed to go back and look at the 2 year old levorphanol samples to determine whether degradation occurred. They will provide free levorphanol levels if they can be obtained from those samples.

8/21/97 Sue Bastaja
Lizzie Sanchez and Lin Chuang

Diskettes were requested by the reviewer for blood concentration data and PK data for total levorphanol in ASCII format **with the data of each subject (seq, period, treatment, C0-Cn, Cmax, AUCT, AUCI, Kel) contained in the same record.** In addition, all data for free levorphanol needs to be submitted in the same arrangement.

x:\new\firmsmz\roxane\telecons\74278

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-278

CORRESPONDENCE

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

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

NDA ORIG AMEND
N/A M

November 10, 1999

Re: ANDA # 74-278 - Amendment
Levorphanol Tartrate Tablets USP, 2 mg

Dear Sir or Madam:

Reference is made to the above mentioned abbreviated new drug application and our Telephone Amendment submitted February 13, 1999. Reference is also made to the fax dated May 29, 1998, from Dr. Holcombe, requesting that Roxane Laboratories tighten the limits for the single and total related substances on the finished product based. A request was also made to revise the stability commitment/ protocol to reflect the changes in the product specifications.

This amendment provides our response to the above requests. Should you have any questions about this supplement, please do not hesitate to contact me. I can be contacted by telephone at (614) 241-4130 or by telefax at (614) 276-0321.

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Sincerely,

Ann M. Maloney

Ann M. Maloney
Director, Drug Regulatory Affairs – Approved Products

APPEARS THIS WAY
ON ORIGINAL

NOV 12 1999

/S/
11-10

Roxane Laboratories, Inc.

February 13, 1998

ORIG AMENDMENT

N/FA

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

Re: ANDA 74-278
Levorphanol Tartrate Tablets USP, 2 mg

TELEPHONE AMENDMENT

Dear Sir or Madame:

Reference is made to the above mentioned abbreviated new drug application, and your telephone call dated .

Enclosed is a response to your request to us to tighten the specifications for Related Compounds. Included in this amendment are the following items:

Application and Certification Statements
Chemistry Deficiency

Please forward this information to the referenced abbreviated new drug application. Correspondence concerning this application should be addressed to Sean Alan F.X. Reade, Director of Regulatory Affairs. I can be contacted by telephone at (614) 276-4000 ext. 2345 or by telefax at (614) 276-0321.

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

Respectfully,

Sean Alan F. X. Reade, M.A.
Director of Regulatory Affairs

RECEIVED
FEB 17 1998
GENERIC DRUGS

Enclosures

P.O. 16532 • Columbus, Ohio 43216-6532 • Phone 614/276-4000 • Telecopier 614/274-0974

Roxane Laboratories, Inc.

TELEFAX

To:	**Mr. Tim Ames, FDA**		
Fax No.:	1-301-443-3839		
From:	Martin J. Williamson		
Tel. No.	614-276-4000 Ext. 2226	**Fax No:**	614-276-0321
Date:	February 13, 1998	**Pages:**	~~20~~ 21 (This page included)
Subject:	**Telephone Amendment to ANDA 74-278 Levorphanol Tartrate Tablets USP, 2mg**		

Dear Mr. Ames

Please find attached a copy of letter I will send to the Document Control Room next Monday, February 16.

Yours truly

Martin J Williamson

Martin J. Williamson

Roxane Laboratories, Inc.

December 19, 1997

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

NEW CORRESP

Re: ANDA 74-278
Levorphanol Tartrate Tablets USP, 2 mg

FACSIMILE AMENDMENT

Dear Sir or Madame:

Reference is made to the above mentioned abbreviated new drug application, and to the facsimile amendment dated November 28, 1997.

Enclosed is a point-by-point response to the requests. Included in this amendment are the following items:

Application and Certification Statements
A. Chemistry Deficiencies

Please forward this information to the referenced abbreviated new drug application. Correspondence concerning this application should be addressed to Sean Alan F.X. Reade, Director of Regulatory Affairs. I can be contacted by telephone at (614) 276-4000 ext. 2345 or by telefax at (614) 276-0321.

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

Respectfully,
Martin J Williamson
for Sean Alan Reade

Sean Alan F. X. Reade, M.A.
Director of Regulatory Affairs

RECEIVED
DEC 2 7 1997
GENERIC DRUGS

Enclosures

P.O. 16532 • Columbus, Ohio 43216-6532 • Phone 614/276-4000 • Telecopier 614/274-0974

FACSIMILE AMENDMENT

NOV 28 1997

ANDA 74-278

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Roxane Labs, Inc. PHONE: 1-800-848-0120

ATTN: Sean Alan Reade FAX: 614-276-0321

FROM: Timothy Ames PROJECT MANAGER (301) 827–5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated November 24, 1992, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levorphanol Tartrate Tablets USP, 2 mg.

Reference is also made to your amendment dated April 29, 1997.

Attached are 1 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

X:\new\ogdadmin\macros\faxfax.frm

S-1

ANDA 74-278

OCT - 9 1997

Roxane Laboratories, Inc.
Attention: Sean Allen Reade
P.O. BOX 16532
Columbus OH 43216

APPEARS THIS WAY
ON ORIGINAL

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Levorphanol Tartrate Tablets, USP, 2 mg.

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

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

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,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 74-278, Original, DUP Jacket
Division File
Field Copy
Chaney
HFD-617 Ames

Letter Out, Bio Acceptable

Endorsements:

L. Sanchez

FINAL PRINT: NC 10-8-97 X:\NEW\FIRMSNZ \ROXANE \LTRS&REV\ 74278 BI2.FAP

APPEARS THIS WAY
ON ORIGINAL

Telephone Conversation Memorandum

ANDA: 74-278

DRUG: Levorphanol Tartrate Tablets USP, 2 mg

FIRM: Roxane, Inc. Martin

PERSONS INVOLVED: Matthew Williamson, Roxane
Tim Ames, FDA

PHONE NUMBER: 614- 654-6258

DATE: January 7, 1998

Called firm at the request of chemistry reviewer, Sema Basaran, to request a tightening of the related compounds limits for single and total impurities.

Informed firm their response to question 2. in the 12/19/97 was unacceptable. The limits they propose are not warranted in terms of the room temperature data submitted. We would consider more reasonable limits to be NMT —for the single largest unknown and NMT — for the total related compounds. If subsequent lot data demonstrates theses limits to be to tight after approval of the ANDA, a post approval supplement could be submitted to that effect. MWilliamson indicated that he would discuss this request with his analytical section. I indicated he should indicate his response as a TELEPHONE AMENDMENT, fax it to my attention, and follow-up with a hard copy. He indicated he would do so.

Timothy W. Ames, R.Ph., M.P.H.
Project Manager, Div Chem II, Branch 6, OGD

/S/

cc: ANDA 74-278
Division file (1)
HFD-617/TAmes/PHONE.163
File: X:\new\firmsnz\roxane\telecons\phone.163

NAI "Bio Response" Bio waiver Jesse 3/28/97

Roxane Laboratories, Inc.

March 17, 1997

NEW CORRESP

Lizzie Sanchez, Pharm.D.
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855

BIOAVAILABILITY
NC/EC

Re: NDA 74-278
Levorphanol Tartrate Tablets USP, 2 mg

Request for Teleconference

Dear Dr. Sanchez:

Reference is made to the above referenced new drug application, and to the Division of Bioequivalence correspondence dated March 5, 1997. Reference is also made to your telephone conversation with Elizabeth A. Ernst, Clinical Research Manager, of Roxane on March 14, 1997 regarding this correspondence. As Elizabeth mentioned Roxane has a concern with comment number one of the March 5, 1997 correspondence. We would like to request a teleconference regarding this comment, if you believe it is necessary.

Reference is made to the following Division of Bioequivalence comment:

"1. In addition to total levorphanol, plasma samples should be assayed for free levorphanol as planned in the protocol."

Response:

Enclosed is correspondence dated June 30, 1995 from Keith K. Chan, Ph.D., Director of the Division of Bioequivalence, to _____. regarding Roxane's proposed bioequivalence protocol for the Levorphanol Tartrate Tablets biostudy. This letter from Dr. Chan contains the following statements regarding the protocol:

> "Measurement of total Levorphanol is considered sufficient for a bioequivalence study. If you want to separately measure the free and conjugated Levorphanol, it would be also acceptable."

Based on this guidance from the Division of Bioequivalence, _____ did not measure the free levorphanol when they conducted the bioequivalence study. They measured only the total levorphanol. The protocol was not amended to reflect this decision with the Division of Bioequivalence, and Roxane apologizes for this oversight.

MAR 18 1997

GENERIC DRUGS

P.O. 16532 • Columbus, Ohio 43216-6532 • Phone 614/276-4000 • Telecopier 614/274-0974

The above is the response Roxane proposes to submit when answering the March 5, 1997 correspondence from the Division of Bioequivalence. If you would please ask the bioequivalence reviewer if this response is sufficient, it would be greatly appreciated. Please contact Elizabeth Ernst, R.N., B.S.N., at 1-800-848-0120, extension 2106, regarding the necessity for a teleconference.

Roxane will have the information necessary to respond to points two, three and four of the March 5, 1997 correspondence by March 24, 1997. If additional assay work must be performed for point one, Roxane needs to know this as soon as possible.

Please forward this information to the referenced new drug application. Thank you very much for your assistance.

Sincerely,

Sue Bastaja

Sue T. Bastaja, R.Ph., J.D.
Manager
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-278

Roxane Laboratories
Attention: Donald H. Chmielewski
P.O. BOX 16532
Columbus, OH 43216

MAR 5 1997

Dear Sir:

Reference is made to the bioequivalence data submitted on August 13, 1996 for Levorphanol Tartrate Tablets USP, 2 mg.

The Office of Generic Drugs has reviewed the submitted bioequivalence data and the following comments are provided for your consideration:

1. In addition to total levorphanol, plasma samples should be assayed for free levorphanol as planned in the protocol.

2. A data diskette containing information of all plasma concentrations of each analyte and the pharmacokinetic parameters of each subject should be submitted.

3. Evidence demonstrating the lack of cross-reactivity in the assay method between levorphanol and naltrexone (or its 6-β-naltrexol metabolite) should be submitted.

4. The clinical records, medical records/case reports of study subjects should be submitted.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

for Nicholas Fleischer, Ph.D.
Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: Date _____
ANDA 74-278, Orig File, Dup File
Div File
Field Copy
HFD-615 PRickman
HFD-650 Sanchez, CST

BIO-LETTER INCOMPLETE

Endorsements:

L. W. Chuang, 3/4/97
Y. C. Huang 3/4/97
L. Sanchez 3/4/97

DRAFTED	LSG	DATE	X:\WPFILE\BIO\74278BIO.D
FINAL PRINT	STM	3/4/97	X:\WPFILE\BIO\FINAL\74278BIO.FST

APPEARS THIS WAY
ON ORIGINAL

Roxane Laboratories, Inc.

September 5, 1997

BIOAVAILABILITY, OGD

N: 18/0

NAI "Bio Amendment, Bio Assigned" 9/11/97

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

Re: ANDA 74-278
Levorphanol Tartrate Tablets USP, 2 mg

BIOEQUIVALENCE AMENDMENT

Dear Sir or Madame:

Reference is made to the above mentioned abbreviated new drug application, and to a telephone conversation between Sue Bastaja of Roxane and Lizzie Sanchez, Pharm.D. and Dr. Chuang of the Division of Bioequivalence on August 22, 1997.

The request in the telephone conversation was the following:

> Please provide an additional data diskette which provides the patient data tabulated per patient rather than per value. The data diskette should also contain the analysis of free levorphanol.

Enclosed in this submission is a data diskette which provides the requested information.

Please forward this information to the referenced abbreviated new drug application.

Correspondence concerning this application should be addressed to Sean Alan F.X. Reade, Director of Regulatory Affairs. I can be contacted by telephone at (614) 276-4000 ext. 2345 or by telefax at (614) 276-4403. In my absence please contact Sue Bastaja at extension 2347.

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

RECEIVED
SEP 11 1997
GENERIC DRUGS

Respectfully,

Sean Alan F. X. Reade, M.A.
Director, Regulatory Affairs

Enclosure, data diskette

P.O. 16532 • Columbus, Ohio 43216-6532 • Phone 614/276-4000 • Telecopier 614/274-0974

Roxane Laboratories, Inc.

June 9, 1997

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

NDA "Bio Assigned" 7/3/97

Re: ANDA 74-278
Levorphanol Tartrate Tablets USP, 2 mg

BIOEQUIVALENCE AMENDMENT

Dear Sir or Madame:

Reference is made to the above mentioned abbreviated new drug application, and to your correspondence dated March 5, 1997.

In response to the points raised in the correspondence, enclosed is a point-by-point response to the requests including data diskettes, case report forms and a clinical report.

Please forward this information to the referenced abbreviated new drug application. Correspondence concerning this application should be addressed to Sean Alan F.X. Reade, Director of Regulatory Affairs. He can be contacted by telephone at (614) 276-4000 ext. 2345 or by telefax at (614) 276-4403.

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 and/or 21 U.S.C., Section 331(j).

Respectfully,

Sue T. Bastaja

Sue T. Bastaja, R.Ph., J.D.
Senior Submissions Specialist
Regulatory Affairs

Enclosure

RECEIVED
JUN 1 [illegible] 1997
GENERIC DRUGS

P.O. 16532 • Columbus, Ohio 43216-6532 • Phone 614/276-4000 • Telecopier 614/274-0974

Roxane Laboratories, Inc.

August 13, 1996

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

BIOAVAILABILITY
NEW CORRESP

RECEIVED
AUG 14 1996
GENERIC DRUGS

Re: NDA 74-278
Levorphanol Tartrate Tablets USP, 2 mg

BIOEQUIVALENCE AMENDMENT

Gentlemen:

Reference is made to the above referenced new drug application and to our amendment dated December 21, 1995. In that correspondence we committed to performing a new bioequivalence study. This amendment contains the final report of that bioequivalence study.

The following bioequivalence study report is submitted for review as demonstration of bioequivalence:

> "A Pharmacokinetic Study to Assess the Bioequivalence of Levorphanol Tartrate 2 mg Tablets (Roxane) with Levo-Dromoran® 2 mg Tablets (Roche) Following Single Dose Administration, in Healthy Subjects Receiving Concomitant Doses of Naltrexone" (2 Volumes)

Please forward this information to the referenced new drug application.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski
Director
Regulatory Affairs

P.O. 16532 • Columbus, Ohio 43216-6532 • Phone 614/276-4000 • Telecopier 614/274-0974

ANDA 74-278

Roxane Laboratories, Inc.
Attention: Donald H. Chmielewski
P.O. 16532
Columbus, OH 43216-6532

Dear Sir:

This is in reference to your abbreviated new drug application dated November 24, 1992, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Levorphanol Tartrate Tablets USP, 2 mg.

Reference is also made to your amendment dated June 16, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. Regarding drug substance:

The ——— DMF # is listed as —— and —— Please clarify (see part A.2.b).

2. Regarding manufacturing and processing:

a. In Part A.4.a. additional testing for alternate assay and related compounds (RC) are provided on pages 72-75. RC I: limit is NMT — area/area relative to Levorphanol Tartrate. RC II limit is NMT — area/area relative to Levorphanol Tartrate. Total related compounds limit is NMT — area/area relative to Levorphanol Tartrate. ——— COA submitted limits for impurity A: —— area% max, and for impurity B: —— area% max and total impurities —— area% max.

Your test results for these related compounds are as follows: Test results for RC I: —— a/a; RC II: ——— a/a and total: —— a/a. Please refer to your response in Part A.2.b. that you will meet ——— area% max limit for total related compounds. Your and the manufacturer's specifications are not consistent. Please provide comment and provide explanation - we strongly suggest tightening your specifications.

d. Please include [redacted] testing and specifications [redacted] SD) in your finished product release specifications.

e. [redacted] and [redacted] wide. They should be tightened.

f. Please provide [redacted] test results on lot 950830 which show that it meets the acceptance criteria [redacted] % with an RSD [redacted]

3. Regarding container/closures:

a. The bottles with [redacted] cap were used for lot 920089. In your amendment dated June 16, 1995 for lot 950830 you submitted 150 cc bottles with [redacted] container/closure systems. Please clarify and explain.

b. Please submit manufacturer's test results for HDPE containers and container/closure systems for tight containers per <661> and <671> USP 23/NF 18.

c. Please provide a DMF number and authorization letter for purified cotton from [redacted]

d. Please update and resubmit your COA for cotton to include [redacted] to comply with USP 23/NF 18 requirements.

4. Regarding laboratory controls:

a. The related compounds limits are too wide. Please refer to your response in Part A.2.b. Your and the manufacturer's related compound specifications are not consistent. Please provide an explanation.

b. Please note that the in vivo biobatch manufactured at the [redacted] for lot 950830 should be submitted to the Division of Bioequivalence and

found acceptable prior to approval of this ANDA.

c. Please include content uniformity limits and test results in your revised finished product COA in Part A.4.f. pages 181-182. Please revise and resubmit.

5. Regarding stability:

a. Please submit 3 months accelerated and available room temperature stability study data for lot 950830 in 150 cc bottles with ——————, cap which is the proposed marketed container/closure system. Include data for unit dose blisters as well.

b. The 150 cc bottles should be placed into the stability protocol and reports. The 60 cc bottles should be deleted from container/closure section, since they are a non-market container/closure system.

c. Please revise your specifications based on the data submitted for related compounds and resubmit revised stability protocols and reports.

d. Please explain why the related compounds test results in unit dose blisters at 36 months is higher than in —— bottles at room temperature in Technical report 1029-23.

e. The related compounds test results in unit dose blister and —— bottles at 24 months for lot 920089 is considerably lower than lots Wa-R-17 and RPO-671 submitted in Part A.7.f. Please explain.

B. Labeling Deficiencies

CONTAINER (For 100's): Satisfactory in draft.

UNIT DOSE CARTON (For 25's): Satisfactory in draft.

UNIT DOSE BLISTER: Satisfactory in draft.

INSERT - Revise as follows:

1. GENERAL COMMENT

Use "μ" rather than "—— throughout the text of the insert (i.e., μ-agonist, μ-opioid).

2. DESCRIPTION

   a. Use "structural formula" rather than "

   b. Last paragraph -

      Each tablet, for oral administration, contains 2 mg levorphanol tartrate dihydrate. In addition, each tablet contains anhydrous lactose,... .

3. CLINICAL PHARMACOLOGY, Clinical Trials, paragraph 2 (second sentence) -

   ...1.5 to 2 mg in three...
   [Delete

4. DOSAGE AND ADMINISTRATION, Use in Chronic Pain (first sentence) -

   ...(See CLINICAL PHARMACOLOGY, Individualization of Dosage).

Please revise your package insert, then prepare and submit final printed labels and labeling. Should further information become available relating to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

> The USP 23/NF 18 is effective from January 1, 1995. The specifications and test methods for drug substance and drug product should be updated to comply with USP 23/NF 18.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond

to all the deficiencies listed. A partial reply to the chemistry and labeling issues will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 12/20/95

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA #74-278
DUP Jacket
Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-647/SBasaran/11-2-95
HFD-647/JSimmons/11-17-95
HFD-613/JGrace/11-29-95
HFD-617/TAmes/12-5-9
74278N02.LSB/disc#6
X:\new\firmsnz\roxane\ltrs&rev\74278.naf
F/T by pah/12-8-95
TYPE OF LETTER: Not Approvable/Major Amendment

12/15/95
12.18.95
12/18/95
12/19/95

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-278

APPEARS THIS WAY ON ORIGINAL

NOV 13 1995

Roxane Laboratories, Inc.
Attention: Donald H. Chmielewski
P.O. BOX 16532
Columbus OH 43216

Dear Sir:

Reference is made to the bioequivalence data submitted on June 16, 1995, for Levorphanol Tartrate Tablets, USP, 2 mg.

The Office of Generic drugs has reviewed the data and the following comments are provided for your consideration:

1. The submitted protocol will not be reviewed, since your correspondence indicated that the study would be initiated July 1, 1995. The Office generally will not review protocols for studies that have been started or concluded. Thus, the Office acknowledges your intentions and will look forward to reviewing the final study when it is submitted for review.

2. The complete dissolution testing contained in the June 16, 1995 submission should be resubmitted with the study report. The dissolution data should compare the test and reference listed drug and be submitted in a comparative side-by-side tabular format for review

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. The submitted study will be classified as a major amendment.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

ANDA 74-278, Original, DUP Jacket
Division File
Field Copy
HFD-600 Reading File
HFD-610 Phillips

Bio-dif

Endorsements:

L. Chuang
YC. Huang
J. Gross

Drafted	STM	10/31/95	X\WPFILE\BIO\N74278D1.APP
Drafted	JAG	10/31/95	X\WPFILE\BIO\N74278D1.APP
FINALIZED	STM	11/01/95	X\WPFILE\BIO\FINAL\N74278.APP

APPEARS THIS WAY
ON ORIGINAL

Roxane Laboratories, Inc.

June 16, 1995

BIOAVAILABILITY

AMENDMENT

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

Re: NDA 74-278
Levorphanol Tartrate Tablets USP, 2 mg

MAJOR AMENDMENT

Gentlemen:

Reference is made to the above mentioned new drug application, and to your correspondence dated June 2, 1993.

In response to the points raised in the correspondence, enclosed is a point-by-point response to the requests as follows:

PART A. CHEMISTRY DEFICIENCIES

1. Reference is made to your statement:

[ ]

Response:

a. [ ]

b. [ ]

P.O. 16532 • Columbus, Ohio 43216-6532 • Phone 614/276-4000 • Telecopier 614/276-8974

GENERIC DRUGS

Redacted 13

pages of

trade secret and/or

confidential

commercial

information

PART C. BIOEQUIVALENCE DEFICIENCIES

Reference is made to your statement:

"C. Bioequivalence Deficiencies"

Response:

Roxane Laboratories, Inc. is committed to fulfilling the requirements of the Agency to obtain application approval. Pursuant to that a new bioequivalence study is scheduled to begin on July 1, 1995 at

A revised Section VI of the application is enclosed with this Part, containing the new protocol, and certificates of analysis (with 12 tablet comparative dissolution profiles) for the test and reference products. Additional testing for this test lot is reported on the COA in the batch record enclosed in Part A.4.a. page 00068.

Please forward this information to the referenced new drug application.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski, R.Ph.
Director
Regulatory Affairs

Roxane Laboratories, Inc. hereby certifies that a "true" copy of this amendment to the application (as described in 314.94(a)(9)) was submitted to the Cincinnati District Office of the FDA at the same time of our original submission of this amendment to the application.

Donald H. Chmielewski

Donald H. Chmielewski

CERTIFIED MAIL - RETURN RECEIPT REQUESTED

ANDA 74-278

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

Dear Madam:

Please refer to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levorphanol Tartrate Tablets USP, 2 mg.

We sent you a "Not Approvable" letter dated June 2, 1993, that detailed deficiencies identified during our reviews. We are unaware of any subsequent correspondence from you that sought to address the outstanding deficiencies.

Absent evidence of interest on the part of an applicant over such a prolonged period can be considered as a request for withdrawal pursuant to the authority cited in Section 314.120(b) of the regulations.

Alternatively, if you do not intend to immediately pursue approval of the application, you may request withdrawal in accord with Section 314.65 of the regulations. If you elect to request withdrawal, it will not prejudice a future filing.

If we do not receive a definitive reply from you within 30 days of the date of this letter in which you request withdrawal or provide substantive amendments to the application that seek to address the deficiencies noted, we will initiate action to administratively withdraw the application.

Please send all correspondence to the following address:

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Sincerely yours,

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-278
Dup Jacket
Division File
HFC-324/MLynch (Approved, Unapproved, Supplements ONLY)
HFD-600/Reading File
Field Copy
HFD-613/labeling **only for labeling supplemental**

Endorsements: HFD-615/PRickman, Acting Chief /S/ 5/31/95 date
HFD-615/WRussell,Reg CS /S/ 5/31/95 date
WP File \russell\74\74-278
F/T by Fox 5/30/95
30-DAY LETTER

/S/
6/1/95

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-278

JUN 2 1993

Roxane Laboratories, Inc.
Attention: Donald H. Chmielewski
P.O. 16532
Columbus, OH 43216

Dear Sir:

This is in reference to your abbreviated new drug application dated November 24, 1992, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Levorphanol Tartrate Tablets USP, 2 mg.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. Regarding composition and components:

2. Regarding drug substance:

3. Regarding other ingredients:

a.

Redacted 3

pages of

trade secret and/or

confidential

commercial

information

B. Labeling Deficiencies

General Comments:

We note the labels for the unit dose blisters were not included in this submission. Please submit for our review and comment.

Container (For 100's) - Revise as follows:

1. USUAL DOSAGE: See Package Insert for...

2. Please comment on the need for the PROTECT FROM MOISTURE statement. We believe a directive such as this should be reserved for those cases where it is truly necessary or the statement will become meaningless due to overuse. We note the innovator does not include this statement and there is no compendial requirement for it.

Unit Dose Carton (For 25's) - Revise as follows:

See comments under Container.

Insert - Revise as follows:

DESCRIPTION

1) Use "molecular formula" [rather than

2) Revise the solubility and descriptive information (paragraph 2) to be in accordance with the USP.

3) Include the route of administration. For example -

Each tablet, for oral administration, contains...

CLINICAL PHARMACOLOGY

1) Revise the two subsection headings, Effect on Respiration and Cardiovascular Effects to appear as the same prominence as the other subsection headings.

2) Effect on Respiration, third sentence, delete-

[redacted]

3) Clinical Trials

Paragraph 2, line 1 - ... of levorphanol tartrate...

4) Individualization of Dosage, paragraph 1, delete everything but the first sentence.

INDICATIONS AND USAGE, revise to read -

Levorphanol Tartrate Tablets are indicated for the management of pain where an opioid analgesic is appropriate.

CONTRAINDICATIONS

Levorphanol Tartrate Tablets are contraindicated in patients allergic to levorphanol.

DOSAGE AND ADMINISTRATION

1) Use in Chronic Pain, line 1 - ... of levorphanol tartrate ...

2) [redacted], delete subsection heading and first sentence and replace with "Note:", for example -

Note: As with all controlled...

Please revise your container labels, carton labeling, and package insert, then prepare and submit final printed labels and labeling. Should further information become available relating to the safety and efficacy of this product, you may be asked to further revise your labeling prior to approval.

C. Bioequivalence Deficiencies:

1. The limit of quantitation, defined by the firm as [redacted], has not been validated since only the concentration range of [redacted] was validated with reliable accuracy and precision.

2. The specificity of the [redacted] was not confirmed by testing for possible interference from other structurally related substances in the plasma.

3. We advise that you employ an analytical method which would permit the accurate measurement of levorphanol at low concentrations. The computation of $AUC_{(0-t)}$ and the estimation of $AUC_{(0-\infty)}$ should always result in the ratio of $AUC_{(0-t)}/AUC_{(0-\infty)}$ greater than 0.80.

4. Information on the procedures for reassays and justification for the values presented in the final report for these repeated samples should be provided.

5. Comparative dissolution testing should be performed on the same lots of both test and reference product as used in the bioequivalence study.

6. The lot size of the test product lot used in any bioequivalence study should be at least ~~~ finished dosage units or — of the largest proposed commercial lot, whichever is greater.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply to the chemistry and labeling issues will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 6/1/93

C. Greg Guyer, Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA #74-278
DUP Jacket
Division File
HFC-130/JAllen
HFD-600/Reading File

Endorsements:

HFD-637/SBasaran/3-11-93 5/24/93 /S/
HFD-637/JSimmons/4-9-93 5.24.93
HFD-638/JGrace/4-28-93 5/24/93
HFD-652/LChuang/ for L.C 5/24/93
HFD-637/TAmes/4-27-93
74278N01.LSB/disc#2
F/T by crc/5-19-93
TYPE OF LETTER: Not Approvable/Major Amendment

/S/ /S/ 5/24/93 /S/ - 6/2/93

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-278

Roxane Laboratories, Inc.
Attention: Donald H. Chmielewski
P.O. 16532
Columbus, OH 43216

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 for the following:

NAME OF DRUG: Levorphanol Tartrate Tablets USP, 2 mg

DATE OF APPLICATION: November 24, 1992

DATE OF RECEIPT: November 24, 1992

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.

Sincerely yours,

/S/

12-10-92

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #74-278
DUP/Division File
HFC-130/JAllen
HFD-637/FFang
HFD-632/ESherwood
HFD-600/Reading File
R/D initialed by WRickma
74278Ack.ltr(acknow)jkg/12-4-92
F/T by bcw/12-7-92
Acknowledgement Letter!

/S/ 12-8-92
/S/ 12-9-92

Roxane Laboratories, Inc.

November 24, 1992

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

Re: Levorphanol Tartrate Tablets USP, 2 mg

ORIGINAL SUBMISSION

Gentlemen:

Enclosed in duplicate is an abbreviated new drug application submitted for the purpose of allowing Roxane Laboratories, Inc. to obtain approval to manufacture, package, and distribute the drug product. This is based upon the October 8, 1992 *Federal Register* DESI Notice for Levo-Dromoran® Tablets [Docket No. 92N-0378; DESI 10520].

The product will be tested according to the enclosed specifications and will be labeled and marketed as Levorphanol Tartrate Tablets USP, 2 mg. Final printed labeling is contained in Section V of this application. Samples will be submitted upon assignment of the NDA number and at the Division's request and direction. The "listed" product is Levo-Dromoran® Tablets (Roche). Results of a bioequivalence study are contained in Volumes 3, 4, and 5 of this submission.

In compliance with the Generic Drug Enforcement Act of 1992, (1) Roxane Laboratories, Inc. hereby certifies that we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connection with this application. (2) There are no convictions of the applicant and affiliated persons responsible for the development or submission of the application.

The methods validation package (three copies) is contained in a separate volume under this cover letter.

Sincerely,

Donald H. Chmielewski

Donald H. Chmielewski, R.Ph.
Director
Regulatory Affairs

DHC
Enclosure

P.O. 16532 • Columbus, Ohio 43216-6532 • Phone 614/276-4000 • Telecopier 614/274-0974