CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

74-597

Generic Name: Hydromorphone Hydrochloride Tablets USP, 8 mg

Sponsor: Roxane Laboratories, Inc.

Approval Date: July 29, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-597

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-597

APPROVAL LETTER

ANDA 74-597

JUL 2[illegible]8

Roxane Laboratories, Inc.
Attention: Sean Alan F. X. Reade
P.O. Box 16532
Columbus, OH 43216-6532

Dear Sir:

This is in reference to your abbreviated new drug application dated December 29, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydromorphone Hydrochloride Tablets USP, 8 mg.

Reference is also made to your amendments dated December 21, 1995; and June 17, 1998.

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 Hydromorphone Hydrochloride Tablets USP, 8 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Dilaudid® Tablets, 8 mg, of Knoll Pharmaceutical Company). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 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/ 7/29/96

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-597

Final Printed Labeling

HYDROMORPHONE HCl
Tablets and Oral Solution C II

ROXANE LABORATORIES, INC.

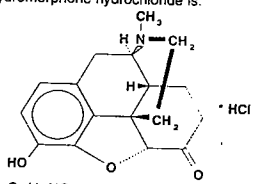
HYDROMORPHONE HYDROCHLORIDE C II
Tablets USP 8 mg and Oral Solution 1 mg per mL

(WARNING: May be habit forming)

DESCRIPTION

Hydromorphone hydrochloride, a hydrogenated ketone of morphine, is a narcotic analgesic.

The chemical name for hydromorphone hydrochloride is Morphinan-6-one, 4,5-epoxy-3-hydroxy-17-methyl-, hydrochloride, (5α)-. The structural formula of hydromorphone hydrochloride is:



$C_{17}H_{19}NO_3 \cdot HCl$ M.W. 321.81

Each tablet, for oral administration, contains 8 mg of hydromorphone hydrochloride. Inactive ingredients: each tablet also contains anhydrous lactose and magnesium stearate.

Each 5 mL (1 teaspoonful), for oral administration, contains 5 mg of hydromorphone hydrochloride. The inactive ingredients are polyethylene glycol 1000, propylene glycol, methylparaben, propylparaben, saccharin sodium, sorbitol, FD & C Red #40, flavor and water.

CLINICAL PHARMACOLOGY

Many of the effects described below are common to this class of mu-opioid agonist analgesics. In some instances, data may not exist to distinguish the effects of hydromorphone from those observed with other opioid analgesics. However, in the absence of data to the contrary, it is assumed that hydromorphone would possess all the actions of mu-agonist opioids.

Opioid analgesics exert their primary effects on the central nervous system and organs containing smooth muscle. The principal actions of therapeutic value are analgesia and sedation. A significant feature of the analgesia is that it can occur without loss of consciousness. Opioid analgesics also suppress the cough reflex and may cause respiratory depression, mood changes, mental clouding, euphoria, dysphoria, nausea, vomiting and electroencephalographic changes.

The precise mode of analgesic action of opioid analgesics is unknown. However, specific CNS opiate receptors have been identified. Opioids are believed to express their pharmacological effects by combining with these receptors.

Opioids depress the cough reflex by direct effect on the cough center in the medulla.

Opioids depress the respiratory reflex by a direct effect on the brain stem respiratory centers. The mechanism of respiratory depression also involves a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension.

Opioids cause miosis. Pinpoint pupils are a common sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings) and marked mydriasis occurs with asphyxia.

Gastric, biliary and pancreatic secretions are decreased by opioids. Opioids cause a reduction in motility associated with an increase in tone in the gastric antrum and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, and tone may be increased to the point of spasm. The end result is constipation. Opioids can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi.

Certain opioids

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Certain opioids produce peripheral vasodilation which may result in orthostatic hypotension. Release of histamine may occur with opioids and may contribute to drug-induced hypotension. Other manifestations of histamine release may include pruritus, flushing, and red eyes.

The dosage of opioid analgesics like hydromorphone should be individualized for any given patient, since adverse events can occur at doses that may not provide complete freedom from pain (see INDIVIDUALIZATION OF DOSAGE).

Pharmacokinetics

In a reported single-dose crossover study in 27 normal subjects the pharmacokinetics of hydromorphone hydrochloride 8 mg tablets were compared to that of 8 mL of hydromorphone hydrochloride oral solution (1 mg/mL). Plasma hydromorphone concentration was determined using a sensitive and specific assay. The pharmacokinetic parameters from this study are outlined below.

Parameter Mean & (CV)	8 mg Tablet	8 mg Oral Solution (1 mg/mL)
C_{max} (ng/mL)	5.5 (33%)	5.7 (31%)
T_{max} (hr)	0.74 (34%)	0.73 (71%)
$AUC_{0-\infty}$ (ng•hr/mL)	23.7 (28%)	24.6 (29%)
$T_{\frac{1}{2}}$ (hr)	2.6 (18%)	2.8 (20%)

Dose proportionality between the 8 mg hydromorphone hydrochloride tablets and other strengths of hydromorphone hydrochloride tablets has not been established.

In normal human volunteers hydromorphone is metabolized primarily in the liver. It is excreted in the urine primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. The effects of renal disease on the clearance of hydromorphone are unknown, but caution should be taken to guard against unanticipated accumulation if renal and/or hepatic functions are seriously impaired. Hydromorphone has been shown to cross placental membranes.

Clinical Trials

Analgesic effects of single doses of hydromorphone hydrochloride oral solution administered to patients with post-surgical pain have been studied in double-blind controlled trials. In one study with 61 patients, both 5 mg and 10 mg of hydromorphone hydrochloride oral solution provided significantly more analgesia than placebo. In another trial with 80 patients, 5 mg and 10 mg of hydromorphone hydrochloride oral solution were compared to 30 mg and 60 mg of morphine sulfate oral liquid. The pain relief provided by 5 mg and 10 mg hydromorphone hydrochloride oral solution was comparable to 30 mg and 60 mg oral morphine sulfate, respectively.

Individualization of Doses

Safe and effective administration of opioid analgesics to patients with acute or chronic pain depends upon a comprehensive assessment of the patient. The nature of the pain (severity, frequency, etiology, and pathophysiology) as well as the concurrent medical status of the patient will affect selection of the starting dosage.

In non opioid-tolerant patients, therapy with hydromorphone is typically initiated at an oral dose of 2 to 4 mg every four hours, but elderly patients may require lower doses (see PRECAUTIONS-Geriatric Use).

In patients receiving opioids, both the dose and duration of analgesia will vary substantially depending on the patient's opioid tolerance. The dose should be selected and adjusted so that at least 3 to 4 hours of pain relief may be achieved. In patients taking opioid analgesics, the starting dose of hydromorphone should be based on the prior opioid usage. This should be done by converting the total daily usage of the previous opioid to an equivalent total daily dosage of oral hydromorphone using an equianalgesic table (see below). For opioids not in the table, first estimate the equivalent total daily usage of oral morphine, then use the table to find the equivalent total daily dosage of hydromorphone.

Once the total daily dosage of hydromorphone has been estimated, it should be divided into the desired number of doses. Since there is individual variation in response to different opioid drugs, only 1/2 to 2/3 of the estimated dose of hydromorphone calculated from equivalence tables should be given for the first few doses, then increased as needed according to the patient's response.

In chronic pain, doses should be administered around-the-clock. A supplemental dose of 5 to 15% of the total daily usage may be administered every two hours on an "as-needed" basis.

Periodic reassessment after the initial dosing is always required. If pain management is not satisfactory and in the absence of significant opioid-induced adverse events, the hydromorphone dose may be increased gradually. If excessive opioid side effects are

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Periodic reassessment after the initial dosing is always required. If pain management is not satisfactory and in the absence of significant opioid-induced adverse events, the hydromorphone dose may be increased gradually. If excessive opioid side effects are observed early in the dosing interval, the hydromorphone dose should be reduced (see CLINICAL PHARMACOLOGY, Individualization of Dosage and PRECAUTIONS). If this results in breakthrough pain at the end of the dosing interval, the dosing interval may need to be shortened. Dose titration should be guided more by the need for analgesia than the absolute dose of opioid employed.

Opioid Analgesic Equivalents With Approximately Equianalgesic Potency*

Nonproprietary (Trade) Name	IM or SC Dose	ORAL Dose
Morphine Sulfate	10 mg	40-60 mg
Hydromorphone Hydrochloride	1.3-2 mg	6.5-7.5 mg
Oxymorphone HCl	1-1.1 mg	6.6 mg
Levorphanol tartrate	2-2.3 mg	4 mg
Meperidine, pethidine HCl	75-100 mg	300-400 mg
Methadone HCl	10 mg	10-20 mg

*Dosages, and ranges of dosages represented, are a compilation of estimated equipotent dosages from published references comparing opioid analgesics in cancer and severe pain.

INDICATIONS AND USAGE

Hydromorphone Hydrochloride Tablets and Oral Solution are indicated for the management of pain in patients where an opioid analgesic is appropriate.

CONTRAINDICATIONS

Hydromorphone Hydrochloride is contraindicated in: patients with known hypersensitivity to hydromorphone, patients with respiratory depression in the absence of resuscitative equipment, and in patients with status asthmaticus. Hydromorphone hydrochloride is also contraindicated for use in obstetrical analgesia.

WARNINGS

Impaired Respiration

Respiratory depression is the chief hazard of hydromorphone. Respiratory depression occurs most frequently in overdose situations, in the elderly, in the debilitated, and in those suffering from conditions accompanied by hypoxia of hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Hydromorphone should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or in patients with preexisting respiratory depression. In such patients even usual therapeutic doses of opioid analgesics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Drug Dependence

Hydromorphone is a Schedule II narcotic. Hydromorphone can produce drug dependence of the morphine type and therefore have the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of hydromorphone, which should be prescribed and administered with the degree of caution appropriate to the use of morphine. Abrupt discontinuance in the administration of hydromorphone in patients who are physically dependent on opioids is likely to result in a withdrawal syndrome (see DRUG ABUSE AND DEPENDENCE).

PRECAUTIONS

Special Risk Patients

In general, opioids should be given with caution and the initial dose should be reduced in the elderly or debilitated and those with severe impairment of hepatic, pulmonary or renal functions; myxedema or hypothyroidism; adrenocortical insufficiency (e.g., Addison's Disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; gall bladder disease; acute alcoholism; delirium tremens; kyphoscoliosis or following gastrointestinal surgery.

The administration of opioid analgesics including hydromorphone may obscure the diagnoses or clinical course in patients with acute abdominal conditions and may aggravate preexisting convulsions in patients with convulsive disorders.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of hydromorphone with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other

intracranial lesions, or preexisting increase in intracranial pressure. Opioid analgesics including hydromorphone may produce effects which can obscure the clinical course and neurologic signs of further increase in intracranial pressure in patients with head injuries.

Hypotensive Effect

Opioid analgesics, including hydromorphone, may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a depleted blood volume, or a concurrent administration of drugs such as phenothiazines or general anesthetics (see also PRECAUTIONS - Drug Interactions). Therefore, hydromorphone should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Use in Ambulatory Patients

Hydromorphone may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients should be cautioned accordingly. Hydromorphone may produce orthostatic hypotension in ambulatory patients. The addition of other CNS depressants to hydromorphone therapy may produce additive depressant effects, and hydromorphone should not be taken with alcohol.

Use in Biliary Surgery

Opioid analgesics including hydromorphone should also be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

Use in Drug and Alcohol Dependent Patients

Hydromorphone should be used with caution in patients with alcoholism and other drug dependencies due to the increased frequency of narcotic tolerance, dependence, and the risk of addiction observed in these patient populations. Abuse of hydromorphone in combination with other CNS depressant drugs can result in serious risk to the patient.

Drug Interactions

The concomitant use of other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers and alcohol may produce additive depressant effects. Respiratory depression, hypotension and profound sedation or coma may occur. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Opioid analgesics, including hydromorphone, may enhance the action of neuromuscular blocking agents and produce an excessive degree of respiratory depression.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals to evaluate the drug's carcinogenic and mutagenic potential or the effects on fertility, have not been conducted.

Pregnancy

Teratogenic Effects: Pregnancy Category C: Literature reports of hydromorphone hydrochloride administration to pregnant Syrian hamsters show that hydromorphone hydrochloride is teratogenic at a dose of 20 mg/kg which is 600 times the human dose. A maximal teratogenic effect (50% of fetuses affected) in the Syrian hamster was observed at a dose of 125 mg/kg (738 mg/m^2). There are no well-controlled studies in women. Hydromorphone hydrochloride is known to cross placental membranes. Hydromorphone should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus (see Labor and Delivery and DRUG ABUSE AND DEPENDENCE).

Labor and Delivery

Hydromorphone is contraindicated in Labor and Delivery (see CONTRAINDICATIONS).

Nursing Mothers

Low levels of opioid analgesics have been detected in human milk. As a general rule, nursing should not be undertaken while a patient is receiving hydromorphone since it, and other drugs in this class, may be excreted in the milk.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Hydromorphone has not been studied in geriatric patients. Elderly subjects have been shown to have at least twice the sensitivity (as measured by EEG changes) of young adults to some opioids. When administering hydromorphone to the elderly, the initial dose should be reduced (see INDIVIDUALIZATION OF DOSAGE and PRECAUTIONS).

ADVERSE REACTIONS

The adverse effects of hydromorphone hydrochloride are similar to those of other agonist opioid analgesics, and represent established pharmacological effects of the drug class. The major hazards include respiratory depression and apnea. To a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest have occurred.

The most frequently observed adverse effects are light-headedness, dizziness, sedation, nausea, vomiting, sweating, flushing, dysphoria, euphoria, dry mouth, and pruritus. These effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain. Syncopal reactions and related symptoms in ambulatory patients may be alleviated if the patient lies down.

Less Frequently Observed with Opioid Analgesics:

General and CNS: Weakness, headache, agitation, tremor, uncoordinated muscle movements, alterations of mood (nervousness, apprehension, depression, floating feelings, dreams), muscle rigidity, paresthesia, muscle tremor, blurred vision, nystagmus, diplopia and miosis, transient hallucinations and disorientation, visual disturbances, insomnia and increased intracranial pressure may occur.

Cardiovascular: Chills, tachycardia, bradycardia, palpitation, faintness, syncope, hypotension and hypertension have been reported.

Respiratory: Bronchospasm and laryngospasm have been known to occur.

Gastrointestinal: Constipation, biliary tract spasm, ileus, anorexia, diarrhea, cramps and taste alteration have been reported.

Genitourinary: Urinary retention or hesitancy, and

intracranial pressure may occur.

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Gastrointestinal: Constipation, biliary tract spasm, ileus, anorexia, diarrhea, cramps and taste alteration have been reported.

Genitourinary: Urinary retention or hesitancy, and antidiuretic effects have been reported.

Dermatologic: Urticaria, other skin rashes, and diaphoresis.

DRUG ABUSE AND DEPENDENCE

Hydromorphone hydrochloride is a Schedule II narcotic similar to morphine. Opioid analgesics may cause psychological and physical dependence (see WARNINGS). Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal symptoms also may be precipitated in the patient with physical dependence by the administration of a drug with opioid antagonist activity, e.g., naloxone (see also OVERDOSAGE).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage, but it may become clinically detectable after as little as a week. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia. In chronic pain patients, and in opioid- tolerant cancer patients, the dose of hydromorphone should be guided by the degree of tolerance manifested.

In chronic pain patients in whom opioid analgesics including hydromorphone are abruptly discontinued, a severe abstinence syndrome should be anticipated. This may be similar to the abstinence syndrome noted in patients who withdraw from heroin. Because of excessive loss of fluids through sweating, or vomiting and diarrhea, patients experiencing the syndrome usually exhibit marked weight loss, dehydration, ketosis, and disturbances in acid-base balance. Cardiovascular collapse can occur. Without treatment most observable symptoms disappear in 5 to 14 days; however, there appears to be a phase of secondary or chronic abstinence which may last for 2 to 6 months characterized by insomnia, irritability, muscular aches, and autonomic instability.

In the treatment of physical dependence on hydromorphone, the patient may be detoxified by gradual reduction of the dosage, although this is unlikely to be necessary in the terminal cancer patient. If abstinence symptoms become severe, the patient may be detoxified with methadone. Temporary administration of tranquilizers and sedatives may aid in reducing patient anxiety. Gastrointestinal disturbances or dehydration should be treated accordingly.

OVERDOSAGE

Serious overdosage with hydromorphone hydrochloride is characterized by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes bradycardia and hypotension. In serious overdosage, particularly following intravenous injection, apnea, circulatory collapse, cardia arrest and death may occur.

In the treatment of overdosage, primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. A potentially serious oral ingestion, if recent, should be managed with gut decontamination. In unconscious patients with a secure airway, instill activated charcoal (30 to 100 g in adults, 1 to 2 g/kg in infants) via a nasogastric tube. A saline cathartic or sorbitol may be added to the first dose of activated charcoal.

Opioid-tolerant Patient

Since tolerance to the respiratory and CNS depressant effects of opioids develops concomitantly with tolerance to their analgesic effects, serious respiratory depression due to an acute overdose is unlikely to be seen in opioid-tolerant patients receiving the usual therapeutic dosage of hydromorphone for chronic pain.

Note: In an individual who is physically dependent on opioids, administration of the usual dose of an opioid antagonist will precipitate an acute withdrawal syndrome. The severity will depend on the degree of physical dependence and the dose of the antagonist administered. If necessary to treat serious respiratory depression in the physically-dependent patient, opioid antagonist should be administered with care and by titration, using fractional (one fifth to one tenth) doses of the antagonist.

Non-tolerant Patient

The opioid antagonist, naloxone, is a specific antidote against respiratory depression which may result from overdosage, or unusual sensitivity to hydromorphone. A dose of naloxone hydrochloride (usually given as a test dose of 0.4 mg, followed by up to 2 mg if needed) should be administered intravenously, if possible, simultaneously with respiratory resuscitation. The dose can be repeated in 3 minutes. Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression. Naloxone should be administered cautiously to persons who are known, or suspected to be physically dependent on hydromorphone (see Opioid-tolerant Patient, above).

Since the duration of action of hydromorphone may exceed that of the antagonist, the patient should be kept under continued surveillance; repeated doses of the antagonist may be required to maintain adequate respiration. Apply other supportive measures when indicated.

Supportive measures (including oxygen, vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

DOSAGE AND ADMINISTRATION

Solution: The usual adult oral dosage of

sors) should be employed [illegible] latory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

DOSAGE AND ADMINISTRATION

Oral Solution: The usual adult oral dosage of hydromorphone hydrochloride oral solution is one-half (2.5 mL) to two teaspoonfuls (10 mL) (2.5 mg - 10 mg) every 3 to 6 hours as directed by the clinical situation. Oral dosages higher than the usual dosages may be required in some patients.

Tablet: The usual starting dose for hydromorphone hydrochloride tablets is 2 mg to 4 mg, orally, every 4 to 6 hours. Appropriate use of the 8 mg tablet must be decided by careful evaluation of each clinical situation.

A gradual increase in dose may be required if analgesia is inadequate, as tolerance develops, or if pain severity increases. The first sign of tolerance is usually a reduced duration of effect.

SAFETY AND HANDLING INSTRUCTIONS

Hydromorphone Hydrochloride Tablets and Oral Solution pose little risk of direct exposure to health care personnel and should be handled and disposed of prudently in accordance with hospital or institutional policy. Significant absorption from dermal exposure is unlikely; accidental dermal exposure to hydromorphone hydrochloride oral solution should be treated by removal of any contaminated clothing and rinsing the affected area with cool water. Patients and their families should be instructed to flush any Hydromorphone Hydrochloride Oral Solution that is no longer needed.

Access to abusable drugs such as Hydromorphone Hydrochloride Tablets and Oral Solution presents an occupational hazard for addiction in the health care industry. Routine procedures for handing controlled substances developed to protect the public may not be adequate to protect health care workers. Implementation of more effective accounting procedures and measures to restrict access to drugs of this class (appropriate to the practice setting) may minimize the risk of self-administration by health care providers.

HOW SUPPLIED

Hydromorphone Hydrochloride Tablets USP
8 mg off-white-colored, round, scored tablets
(Tablets Identified 54 403)
NDC 0054-8370-24: Unit dose, 25 tablets per card (reverse numbered), 4 cards per shipper.
NDC 0054-4370-25: Bottles of 100 tablets.

Hydromorphone Hydrochloride Oral Solution
5 mg per 5 mL, red-colored,
raspberry-flavored solution
NDC 0054-8349-16: Unit Dose Patient Cups™ filled to deliver 4 mL (4 mg hydromorphone hydrochloride), ten 4 mL Patient Cups™ per shelf pack, four shelf packs per shipper.
NDC 0054-8350-16: Unit Dose Patient Cups™ filled to deliver 8 mL (8 mg hydromorphone hydrochloride), ten 8 mL Patient Cups™ per shelf pack, four shelf packs per shipper.
NDC 0054-3387-50: Bottles of 120 mL.
NDC 0054-3387-58 Bottles of 250 mL.
NDC 0054-3387-63: Bottles of 500 mL.

Storage: Hydromorphone Hydrochloride Tablets and Oral Solution should be stored between 59°-77°F (15°-25°C). Protect from light.

A schedule II Narcotic DEA Order Form is required.

Revised October 1997

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Roxane
Laboratories, Inc.
Columbus, Ohio 43216

Usual Dosage: See Package Insert for Complete Prescribing Information.

Store between 15°-25°C (59°-77°F)

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

TABLETS IDENTIFIED 54 403
(Side One) 54 403 (Side Two)
DO NOT USE UNLESS TABLETS CARRY THIS IDENTIFICATION

NDC 0054-4370-25 100 Tablets

8 mg CII

HYDROMORPHONE
Hydrochloride
Tablets USP

Each tablet contains Hydromorphone Hydrochloride 8 mg
(Warning: May be habit forming.)
Caution: Federal law prohibits dispensing without prescription.

Roxane Laboratories, Inc. Columbus, Ohio 43216

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Usual Dosage: See Package Insert for Complete Prescribing Information.

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74-597

CSO LABELING REVIEW(S)

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

ANDA Number: 74-597

Date of Submission: June 25, 1997

Applicant's Name: Roxane Laboratories, Inc.

Established Name: Hydromorphone Hydrochloride Tablets USP, 8 mg

Labeling Deficiencies:

1. CONTAINER:

   a. 100s

      Add the statement "(WARNING: May be habit forming)" immediately beneath the established name. We refer you to 21 CFR 329.10(c) for further guidance.

   b. Unit dose blister

      Satisfactory in draft. However we note that your unit dose blister is not light-resistant. The USP storage requirement for this drug product states "Preserve in tight, light-resistant containers."

      Since it is possible that the unit dose blister may be separated from its light-resistant cartoning, we request that you provide unit dose blister packaging which meets the USP requirements.

2. CARTON/UNIT DOSE BLISTER CARD: 25s

   See comment 1(a) under CONTAINER.

3. INSERT

   a. Title

      Relocate the statement "(WARNING: May be habit forming)" to appear immediately beneath the established name in the title. In addition, we encourage you to add this statement following the established name at the very top of your insert beneath the bar code.

b. General Comment

We encourage you to use consistent format for the subsection headings under CLINICAL PHARMACOLOGY and PRECAUTIONS sections.

c. DESCRIPTION

In the second paragraph relocate the comma printed on the third line, to appear on the same line as "... 17-methyl- ...".

d. CLINICAL PHARMACOLOGY

i. In the first sentence of the first paragraph add a hyphen between "mu" and "opioid".

ii. Pharmacokinetics

Upon further review, we request you to revise the first paragraph to read as follows:

In a reported single-dose crossover study in 27 normal subjects the pharmacokinetics of hydromorphone hydrochloride 8 mg tablets were compared to that of 8 mL of hydromorphone hydrochloride oral solution (1 mg/mL). Plasma ... assay. The pharmacokinetic parameters from this study are outlined below.

iii. Clinical Trials

Revise [redacted] to read "hydromorphone hydrochloride oral solution".

iv. Individualization of dosage

A) Make the following revisions in the table:

- Revise [redacted] to read "Oxymorphone HCl"
- Revise [redacted] to read "Levorphanol tartrate"
- Revise [redacted] to read "Meperidine, pethidine HCl"
- Revise [redacted] to read "Methadone HCl".

B) The decimal points printed in the table are barely visible. Especially, the decimal point printed for the "IM or SC" dosage range of Levorphanol tartrate.

Please note that [redacted] appears to read "2-23". We encourage you to increase the readability of the decimal points throughout the table.

v. Revise the last sentence of the section to read, "... should be reduced (see CLINICAL PHARMACOLOGY, Individualization of Dosage and PRECAUTIONS)".

e. PRECAUTIONS (Pregnancy: Teratogenic Effects)

Revise [redacted] to read "hydromorphone hydrochloride" in this subsection, except in the last sentence.

f. DOSAGE AND ADMINISTRATION

Oral solution

Revise to read as follows:

The usual adult oral dosage of hydromorphone hydrochloride oral solution is ... 10 mg) every 3 ...

g. SAFETY AND HANDLING INSTRUCTIONS

Revise the first paragraph to read, "... is unlikely; accidental dermal exposure to hydromorphone hydrochloride oral solution should be treated ...".

Please revise your labels and labeling, as instructed above, and submit container labels, carton and package insert labeling in final print.

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

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

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-597

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 1

2. ANDA # 74-597

3. NAME AND ADDRESS OF APPLICANT

Roxane Laboratories, Inc.
P.O. Box 16532
Columbus, OH 43216-6532

4. LEGAL BASIS for ANDA SUBMISSION

Innovator Drug: Dilaudid-HP^{R}; Knoll Pharmaceuticals.

Patent: None
Exclusivity: expires 12-7-95/New chemical entity

5. SUPPLEMENT(s) None

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Hydromorphone Hydrochloride Tablets USP

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

9. AMENDMENTS AND OTHER DATES:

Firm:

12-29-94: Original submission **Subject of this review**
1-26-95: Amendment

FDA:

1-20-95: Refuse to file
3-8-95: Acceptable for filing

10. PHARMACOLOGICAL CATEGORY

Narcotic analgesic

11. Rx or OTC

R_x

12. RELATED IND/NDA/DMF(s)

DMF
DMF
DMF
DMF
DMF

All LOAs are OK.

13. DOSAGE FORM

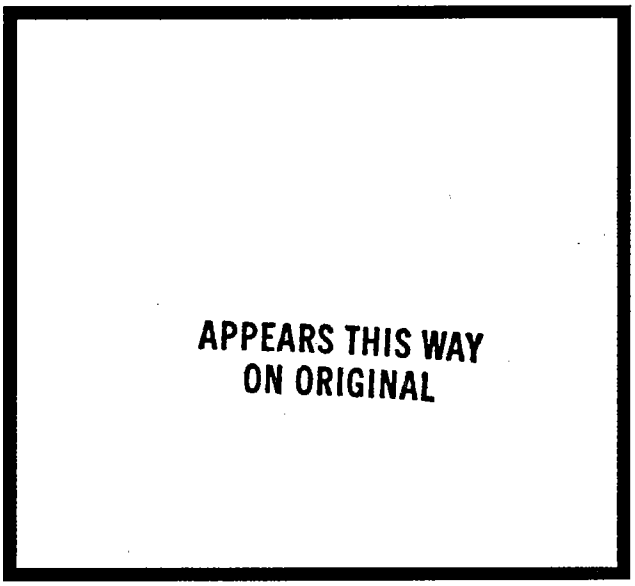
Tablets

14. POTENCY

8 mg

15. CHEMICAL NAME AND STRUCTURE

Hydromorphone Hydrochloride USP ($C_{17}H_{19}NO_3$.HCl) is chemically designated Morphinan-6-one, 4,5-epoxy-3-hydroxy-17-methyl-,hydrochloride, (5α)-, and is represented by the following structural formula:



Molecular weight: 321.81

16. RECORDS AND REPORTS

None

17. COMMENTS

1. Revise components and composition statement
2. Revise drug substance and raw materials.
3. Revise formulation in batch records.
4. Revise manufacturing process.
5. Revise container/closure system.
6. Revise analytical methodology for finished product and degradation products.
7. Revise stability data and stability protocol.
8. Revise labeling information.

Status:

a. **EER:** Pending

Requested for Roxane and [redacted] by L Tang on 6-1-95.

b. **MV** (method validation): N/A

Methods validation is not required since active ingredients and drug product are monographs in USP.

c. **Bio-Review:** Pending, has not been assigned to any reviewer yet.

d. **Labeling review: Not satisfactory**

Not satisfactory per A Vezza reviewed on 5-16-95.

e. **DMF: Satisfactory**

DMF [redacted] has been reviewed and found acceptable by U. V. Venkataram on 4/27/95.

18. CONCLUSIONS AND RECOMMENDATIONS

The application has chemistry and labeling deficiencies and is NOT APPROVABLE.

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 6-1-95

APPEARS THIS WAY
ON ORIGINAL

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1. CHEMIST'S REVIEW NO. 2

2. ANDA # 74-597

3. NAME AND ADDRESS OF APPLICANT

Roxane Laboratories, Inc.
P.O. Box 16532
Columbus, OH 43216-6532

4. LEGAL BASIS for ANDA SUBMISSION

Innovator Drug: Dilaudid-HP^{R}; Knoll Pharmaceuticals.

Patent: None
Exclusivity: expires 12-7-95/New chemical entity

5. SUPPLEMENT(s) None

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Hydromorphone Hydrochloride Tablets USP

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

9. AMENDMENTS AND OTHER DATES:

Firm:

12-29-94: Original submission **Subject of this review**
1-26-95: Amendment
12-22-95 Amendment

FDA:

1-20-95: Refuse to file
3-8-95: Acceptable for filing
6-25-95: 1st NA letter

10. PHARMACOLOGICAL CATEGORY

Narcotic analgesic

11. Rx or OTC

R_x

12. RELATED IND/NDA/DMF(s)

All LOAs are OK.

13. DOSAGE FORM

Tablets

14. POTENCY

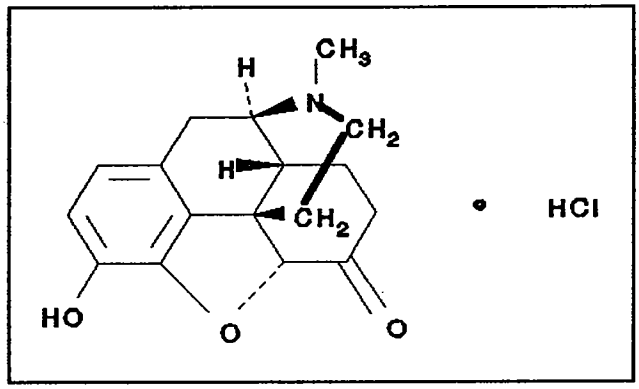
8 mg

15. CHEMICAL NAME AND STRUCTURE

Hydromorphone Hydrochloride USP ($C_{17}H_{19}NO_3$.HCl) is chemically designated Morphinan-6-one, 4,5-epoxy-3-hydroxy-17-methyl-,hydrochloride, (5α)-, and is represented by the following structural formula:

Hydromorphone Hydrochloride USP

$C_{17}H_{19}NO_3$.HCl; M.W. = 321.81



4,5α-Epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride.
CAS [71-68-1]

16. RECORDS AND REPORTS

None

17. COMMENTS

1. Regarding drug substance:

Q: a. The manufacturing site for the drug substance, Hydromorphone Hydrochloride USP, submitted on page 60 of the original submission is incorrect. Please provide the correct address of the manufacturing site for the drug substance.

pgs 3 to 7
mfg

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Requested for Roxane and [redacted] by L Tang on 6-1-95.

b. MV (method validation): N/A

Methods validation is not required since active ingredients and drug product are monographs in USP.

c. Bio-Review: Not Satisfactory

Not Satisfactory per P. Sathe reviewed on 11-14-95.

d. Labeling review: Not satisfactory

Not satisfactory per J Grace reviewed on 7-8-96.

e. DMF: Satisfactory

DMF [redacted] has been reviewed and found acceptable by U. V. Venkataram on 4/27/95.

18. CONCLUSIONS AND RECOMMENDATIONS

The application has chemistry and labeling deficiencies and is NOT APPROVABLE.

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 6-12-96

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1. CHEMIST'S REVIEW NO. 3

2. ANDA # 74-597

3. NAME AND ADDRESS OF APPLICANT

Roxane Laboratories, Inc.
P.O. Box 16532
Columbus, OH 43216-6532

4. LEGAL BASIS for ANDA SUBMISSION

Innovator Drug: Dilaudid-HP^{R}; Knoll Pharmaceuticals.

Patent: None
Exclusivity: expired 12-7-95/New chemical entity

5. SUPPLEMENT(s) None

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Hydromorphone Hydrochloride Tablets USP

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

9. AMENDMENTS AND OTHER DATES:

Firm:

12-29-94: Original submission
1-26-95: Amendment
12-22-95: Amendment
6-25-97: Amendment

FDA:

1-20-95: Refuse to file
3-8-95: Acceptable for filing
6-25-95: 1st NA letter
7-25-96: 2nd NA letter

10. PHARMACOLOGICAL CATEGORY

Narcotic analgesic

11. Rx or OTC

R_x

12. RELATED IND/NDA/DMF(s)

DMF
DMF
DMF
DMF
DMF
DMF

[redacted]

All LOAs are OK.

13. DOSAGE FORM

Tablets

14. POTENCY

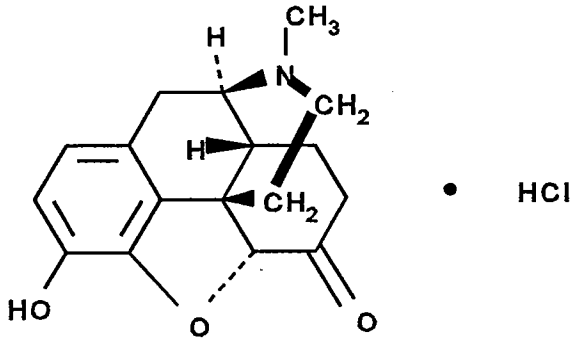
8 mg

15. CHEMICAL NAME AND STRUCTURE

Hydromorphone Hydrochloride USP ($C_{17}H_{19}NO_3$.HCl) is chemically designated Morphinan-6-one, 4,5-epoxy-3-hydroxy-17-methyl-,hydrochloride, (5α)-, and is represented by the following structural formula:

Hydromorphone Hydrochloride USP

$C_{17}H_{19}NO_3$.HCl; M.W. = 321.81



4,5α-Epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride.
CAS [71-68-1]

16. RECORDS AND REPORTS

None

17. COMMENTS

Q: 1. Please provide the street address of the manufacturing site for the drug substance, Hydromorphone Hydrochloride for the purpose of inspection.

A: OK (see response 1 of the 6-25-97 amendment).

Q: 2. We note that Hydromorphone Hydrochloride is affected by light as per USP 23 and Remington's Pharmaceutical Sciences. Please include the

operation procedures and precautions necessitated by the light sensitivity of the active ingredient.

A: OK (see response 2 of the 6-25-97 amendment).

Q: 3. A certification from [redacted] submitted in Part A.4.a. of your December 22, 1995 amendment is incomplete. Please submit available data for the amber glass bottle per USP 23.

A: We note that the manufacturer of the container/closure system used for this application has been changed from [redacted] Please withdraw the container/closure system manufactured from [redacted]

Q: 4. Submit actual test results to demonstrate that the unit dose (blister) package meets the current USP 23 requirements for light-resistant containers.

1. The data presented is not sufficient to demonstrate product stability in blister package. To demonstrate light stability we would require either real time data or accelerated stability data where the product in blister package is exposed to [redacted] Please comment.

2. Please note that the blister card container is only a secondary packaging system. The blister will be unprotected from light when removed from the secondary package. Hence, a non-light resistant blister will be unacceptable. Please comment.

3. Additionally, USP 23 and your package insert require the product to be stored in light-resistant package. We recommend that you comply with this requirement.

4. We have additional concerns that this non-light resistant blister package may confuse issues for the pharmacist regarding substitution.

For all the above reasons we strongly recommend that you consider including a light-resistant blister package.

We cannot reach a conclusion regarding the proposed 2 years expiration date for the unit dose blisters package based on your 3 month room temperature stability data. We would require 24 month room temperature light conditions stability data to grant this expiration date.

Q: 5. Your assay test will not indicate whether Hydromorphone HCl has undergone [redacted] during the stability study. Please include a test

and specification for the ——————— of Hydromorphone Hydrochloride in the product release specifications and stability studies protocol.

A: OK (see response 5 of the 6-25-97 amendment).

Status:

a. **EER:** Satisfactory

Requested for Roxane and ——————————— by L Tang on 6-1-95 and found acceptable on 12-18-96.

b. **MV** (method validation): N/A

Methods validation is not required since active ingredients and drug product are monographs in USP.

c. **Bio-Review:** Satisfactory

Satisfactory per P. Sathe reviewed on 9-3-96.

d. **Labeling review: Not satisfactory**

Not satisfactory per J White reviewed on 8-6-97.

e. **DMF: Satisfactory**

DMF —— has been reviewed and found acceptable by L.Tang on 2-12-97.

18. CONCLUSIONS AND RECOMMENDATIONS

The application has chemistry and labeling deficiencies and is NOT APPROVABLE.

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 8-26-97

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There is no Chemist’s Review #4

1. CHEMIST'S REVIEW NO. 5

2. ANDA # 74-597

3. NAME AND ADDRESS OF APPLICANT

Roxane Laboratories, Inc.
P.O. Box 16532
Columbus, OH 43216-6532

4. LEGAL BASIS for ANDA SUBMISSION

Innovator Drug: Dilaudid-HP^{R}; Knoll Pharmaceuticals.

Patent: None
Exclusivity: expired 12-7-95/New chemical entity

5. SUPPLEMENT(s) None

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Hydromorphone Hydrochloride Tablets USP

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

9. AMENDMENTS AND OTHER DATES:

Firm:

12-29-94: Original submission
1-26-95: Amendment
12-22-95: Amendment
6-25-97: Amendment
10-22-97: Amendment
11-18-97: Amendment (Telephone Amendment and revised master formula card)
11-25-97: Amendment (Telephone Amendment)

FDA:

1-20-95: Refuse to file
3-8-95: Acceptable for filing
6-25-95: 1st NA letter
7-25-96: 2nd NA letter
9-29-97: 3rd NA letter
11-6-97: 4th NA letter (Telephone NA conversation)
11-20-97: 5th NA letter (Telephone NA conversation)

10. PHARMACOLOGICAL CATEGORY

Narcotic analgesic

11. Rx or OTC

R_x

12. RELATED IND/NDA/DMF(s)

DMF
DMF
DMF
DMF
DMF
DMF
All LOAs are OK.

13. DOSAGE FORM

Tablets

14. POTENCY

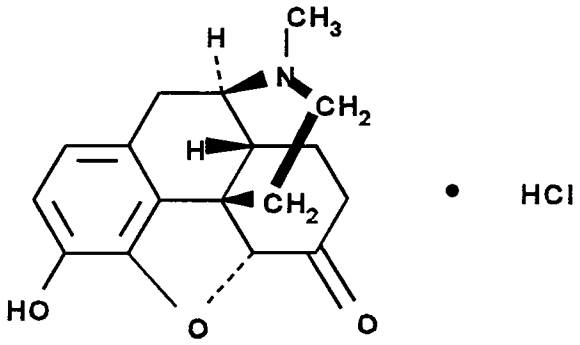
8 mg

15. CHEMICAL NAME AND STRUCTURE

Hydromorphone Hydrochloride USP ($C_{17}H_{19}NO_3$.HCl) is chemically designated Morphinan-6-one, 4,5-epoxy-3-hydroxy-17-methyl-hydrochloride, (5α)-, and is represented by the following structural formula:

Hydromorphone Hydrochloride USP

$C_{17}H_{19}NO_3$.HCl; M.W. = 321.81



4,5α-Epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride.
CAS [71-68-1]

16. RECORDS AND REPORTS

None

17. COMMENTS

2nd NA letter dated 7-25-96 as follows:

Q: 1. The data presented is not sufficient to demonstrate product stability in blister package. To demonstrate light stability we would require either real time data or accelerated stability data where the product in blister package is exposed to such conditions as recommended in the ICH document "Photostability Testing of New Drug Substances and Products". Please comment.

A: OK (withdrawn, see response 1 of the 10-22-97 amendment).

Q: 2. Please note that the blister card container is only a secondary packaging system. The blister will be unprotected from light when removed from the secondary package. Hence, a non-light resistant blister will be unacceptable. Please comment.

A: OK (withdrawn, see response 1 and 2 of the 10-22-97 amendment).

Q: 3. Additionally, USP 23 and your package insert require the product to be stored in light-resistant package. We recommend that you comply with this requirement.

A: OK (withdrawn, see response 1 and 3 of the 10-22-97 amendment).

Q: 4. We have additional concerns that this non-light resistant blister package may confuse issues for the pharmacist regarding substitution.

A: OK (withdrawn, see response 1 and 4 of the 10-22-97 amendment).

For all the above reasons we strongly recommend that you consider including a light-resistant blister package.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Q: We note that the manufacturer of the container/closure system used for this application has been changed from [redacted] Please withdraw the container/closure system manufactured from [redacted]

A: OK (withdrawn, see response B of the 10-22-97 amendment). 4th NA letter from telephone conversation between Tim Ames of the Office of Generic Drugs and Sue Bastaja of Roxane on November 6, 1997 are stated as follows:

Tim Ames called firm to request commitment regarding the new container/closure system for this product.
Tim Ames explained that the recent request to withdraw the original container/closure system (CCS)(due to the discontinuation by the manufacturer) left the application without any stability data, as the firm had not submitted any stability data with the June 25, 1997 minor amendment. The firm acknowledged this point.

As a result Tim Ames requested the firm provide the following:

1. A commitment (prior to the approval of the original ANDA) to demonstrate equivalency between the original CCS and the new CCS as a post-approval supplemental application filed as an Expedited Review Request, with the stipulation that the product would not be marketed until the supplemental application demonstrating the equivalency had been approved.

2. To provide (prior to the approval of the original ANDA) a protocol to be reviewed that would be used post-approval to demonstrate the equivalency between the two CCSs.

3. The protocol should include for the provision of accelerated stability data from one validation lot in the new CCS, and torque testing on both the application and removal of the closure done on the validation batch using the CCS.

The firm was also given the option to provide this data (stability and torque testing) as an amendment to the unapproved original ANDA if they choose rather than providing it post approval.

We asked for a commitment from Roxane that they will put the validation batch on accelerated stability in the new packaging system, submit the data in a supplement with expedited review status and not market the product until the supplement is approved. **Firm have refused.**

5th NA letter from telephone conversation between Tim Ames of the Office of Generic Drugs and Sue Bastaja of Roxane on November 11, 1997 are stated as follows:
Called firm to inform them that the proposals submitted November 17, 1997 regarding the container/closure system (CCS was unacceptable. Tim indicated that we need to have the commitments and data to establish the product's stability and thereby allow for the 24 month expiration date. Tim indicated that Tim did not think this was a negotiable point and that we could not move

toward approval without either stability data in the new CCS or the commitments plus post-approval submissions as outlined in the 11-6-97 teleconference. Tim indicated he could direct any further discussions about this issue to the Division of Chemistry II director, Dr. Frank Holcombe, if necessary. Firm (Sean Alan F.X. Reads, Roxan) indicated he'd get back to us after internal discussions.

November 25, 1997:

[redacted] commits to provide closure [redacted] and accelerated stability data at 1, 2, 3 months for the first validation batch of the drug product in the new container/closure system. Closures on Roxane's packaging lines are applied so that the [redacted] specification is met. [redacted] is the critical parameter measured for the application of the child-resistant closure, rather than the application [redacted] which is actually a function of the [redacted] The [redacted] and stability data will be submitted as a prior-approval supplement after the application is approved along with a request for expedited approval. We have agreed to grant the request for expedited approval as we requested this method of submission. Roxane hereby agrees not to release the drug product for commercial sale in the new container/closure system until the FDA has reviewed and approved the supplement under expedited review.

Status:

a. **EER:** Satisfactory

Requested for Roxane and [redacted] by L Tang on 6-1-95 and found acceptable on Dec. 18, 1996.

b. MV (method validation): N/A

Methods validation is not required since active ingredients and drug product are monographs in USP.

c. Bio-Review: Satisfactory

Satisfactory per P. Sathe reviewed on 9-3-96.

d. Labeling review: Satisfactory

Satisfactory per A. Vezza reviewed on 11-10-97.

e. DMF: Satisfactory

DMF [redacted] has been reviewed and found acceptable by L. Tang on 2/12/97.

18. CONCLUSIONS AND RECOMMENDATIONS

APPROVAL.

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 12-5-97

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ANDA APPROVAL SUMMARY

ANDA: 74-597

DRUG PRODUCT: Hydromorphone Hydrochloride Tablets USP

FIRM: Roxane Laboratories, Inc.

DOSAGE FORM: Tablets

STRENGTHS: 8 mg

CGMP STATEMENT/EIR UPDATE STATUS:

Manufacturer-Finished Dosage Form :

The drug product is manufactured, controlled and processed, packaged, labeled, Testing and stability testing will be conducted at:

Roxane Laboratories, Inc.
1809 Wilson Road
Columbus, OH 43228
(OK on 12-18-96).

Manufacturer-Active Ingredients:

The drug substance is manufactured and supplied by:

[ ]

Contract Laboratories:

[ ]

BIO STUDY:

Satisfactory per P. Sathe reviewed on 9-3-96.

The bioequivalence study conducted by Roxane Labs on its Hydromorphone HCl 8 mg Tablet, lot # 949053 comparing it to Knoll's Dilaudid, 8 mg tablet, lot #11200023 has been found acceptable by the Division of Bioequivalence.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Active drug substance and drug dosage form are both compendial items per USP XXII. Samples will not be requested for testing by FDA labs.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Stability protocol: Satisfactory

Expiration Dating:

24 months expiration date with 3 month room temperature data (25°C) and 3 month accelerated stability data (40°C/ 75%RH) on Lot 949053 (unscored) for amber glass bottles package (old container/closure system - **withdrawn**, 2 ounce square amber glass bottle manufactured by [redacted]

Roxane Laboratories commits to provide closure [redacted] and accelerated stability data at 1, 2, 3 months for the first validation batch of the drug product in the new container/closure system on 11-25-97 Amendment.

Roxane hereby agrees not to release the drug product for commercial sale in the new container/closure system until the FDA has reviewed and approved the supplement under expedited review.

LABELING:

Satisfactory per A. Vezza reviewed on 11-10-97.

STERILIZATION VALIDATION (IF APPLICABLE):

N/A

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

Batch size (bio batch):

a. [redacted] tablets (executed batches #949053, unscored, Bio study), p.115-153 of original submission
b. [redacted] tablets (executed batches #949086, scored compare to list drug), p.270-287 of original submission.

DMF [redacted] has been reviewed and found acceptable by L. Tang on 2/12/97.

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

The batch size for the stability batch is the same as bio batch and stated as follows:

[redacted] tablets (executed batches #949053, unscored, Bio study), p.115-153 of original submission

OPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS O/STABILITY?:

The proposed production batch (blank batch):

_____ tablets (blank batch record), p. 102-114 of the original submission.

CHEMIST: Lucia C. Tang DATE: 12-5-97 12-18-97

SUPERVISOR: Ubrani Venkataram DATE: 12-8-97

U.V. Venkataram 12/18/97

74597AAP.P/Tang/12-5-97

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-597

BIOEQUIVALENCE REVIEW

AUG 27 1996

Hydromorphone Hydrochloride
8 mg Tablet
ANDA 74-597
Reviewer: Pradeep M. Sathe, Ph.D.
WP #74597O.D95

Roxane Labs.
Columbus, Ohio-43216
Submission Date:
December 21, 1995

REVIEW OF A BIO-EQUIVALENCE STUDY AMENDMENT

BACKGROUND : The firm had originally submitted an application for the above drug moiety on December 29, 1994. The application consisted of a a single dose fasting bio-equivalency study and dissolution testing methodology and data comparing 8 mg test (Roxane) and reference (Knoll's Dilaudid^{R}) tablet formulations. The application was found to be deficient with respect to certain study related information. The firm was notified regarding the comments and deficiencies on November 14, 1995. The current amendment consists of the firm's responses to Division's comments and deficiencies. The Division comment/deficiency, firm's response and Division response are given in that order.

Division Comment :

The original protocol (Page 7) specified that, the sampling scheme is (0)hr and 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0 and 24.0hr post-dose, which appears to be reasonable based on the PDR reported $T_{1/2}$. On page 2, the sampling scheme is modified to (0)hr pre-dose and 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0 and 48.0hr post-dose. If the $T_{1/2}$ is about 2hr, why was the sampling scheme extended up to 48hr? Were you aware of the longer $T_{1/2}$ before the study started? If not, why was the sampling extended? Please respond.

Firm's Response :

The protocol was amended to the 48 hr sampling scheme in response to information obtained from analysis of a previous hydromorphone study in which a 4 mg oral solution dose was administered. This study suggested that based on our current assay method sensitivity, the half-life was much longer than 2 hours (i.e. in the 20-30 hour range). Thus the study sampling time was modified for the 8 mg tablet dose.

Division Response :

Since the study has already been completed, firm's response is acceptable.

Division Deficiency :

Subject #8 showed hydromorphone levels at -1.0hr for the reference treatment. Was it due to assay anomaly? Can it bias the analysis? Please comment. The data should be reanalyzed excluding subject #8

who showed detectable levels in the first leg of the study.

Firm's Response :

The hydromorphone levels at -1.0 hr was confirmed by reassays and shown to be not an assay anomaly. Clinical records were checked for a possible non-compliance.

We have taken out subject #8 data and reanalyzed. The PK data without subject #8 are enclosed in this part for your review. Subject #3 and 8 have been excluded and replaced with subject #25 and 26 in the data analysis.

Division's Response :

Firm's reanalysis data was reevaluated by the reviewer and is found to be acceptable with respect to the pharmacokinetic parameters and the outcome. The newly calculated pharmacokinetic parameters (without subject #8 data) are given in tables A and B. The Cmax units are ng/ml, AUC units are mg/ml*hr, Tmax and Half-life units are hr and Kel units are (1/hr).

Table A : Mean pharmacokinetic parameters excluding subject #8 data calculated with respect to 48 hour sampling

Parameter	Test (Roxane)	Reference (Knoll)	90% Confidence Interval	(T/R) Mean Ratio
Cmax	3.531	3.980	81.7-95.7	
Tmax	1.041	0.972	----	
AUC(0-t)	22.803	24.668	87.9-96.9	
AUC(0-inf)	31.270	32.672	83.2-108.2	
Kel	0.029	0.029	----	
$T_{1/2}$	29.163	30.723	----	
LnCmax, Geometric Mean	1.207, 3.343	1.337, 3.808	80.1-96.2	87.8
LnAUC(0-t), Geometric Mean	3.101, 22.22	3.180, 24.05	87.8-97.2	92.4
LnAUC(0-inf), Geometric Mean	3.387, 29.58	3.457, 31.72	83.9-103.4	93.2

Table B : Mean pharmacokinetic parameters excluding subject #8 data calculated with respect to 8 hour sampling

Parameter	Test (Roxane)	Reference (Knoll)	90% Confidence Interval	(T/R) Mean Ratio
Cmax	3.531	3.980	81.7-95.7	
Tmax	1.041	0.972	----	
AUC(0-t)	10.816	12.326	82-93.5	
AUC(0-inf)	12.536	14.223	82.7-93.5	
Kel	0.287	0.281	----	
$T_{1/2}$	2.53	2.61	----	
LnCmax, Geometric Mean	1.207, 3.343	1.337, 3.808	80.1-96.2	87.8
LnAUC(0-t), Geometric Mean	2.3498, 10.48	2.4765, 11.90	82-94.7	88.1
LnAUC(0-inf), Geometric Mean	2.4963, 12.14	2.6178, 13.71	83-94.5	88.5

It could be seen that the the 90% confidence intervals of the mean parameter differences are within the limits of 80-125% implying pharmacokinetic equivalence of the two formulations. It is noted that parameter LnCmax bearly passes the acceptance limit in table A.

Division Deficiency :

Please explain why the dissolution absorbance is measured at ——— instead of ——— as stated in the USP.

Firm's Response :

The dissolution absorbance for the 12 tablet profiles was measured at ——— instead of ——— because Roxane's alternate method for analyzing dissolution samples was used rather than the USP method. The USP method is a ——————— procedure and samples are read at ——— The alternate method is a ——procedure and samples are read at ——— A study was done comparing the USP method and the alternate method. The data confirmed that both methods are suitable for analyzing dissolution samples. The Technical Reports which validate the dissolution procedures are enclosed as follows: (These

reports were not part of the Bioequivalence volumes supplied at the time of initial submission, since they appeared in Section XVI.)

1. Technical Report No. 0944-26
"Comparison of the USP assay and alternate assay method for hydromorphone hydrochloride tablets USP, 8 mg"

2. Technical Report No. 0944-20
"Validation of the USP dissolution method for hydromorphone hydrochloride tablets USP, 8 mg"

3. Technical Report No. 0944-19
"Validation of an alternate dissolution method for hydromorphone hydrochloride tablets USP, 8 mg"

4. Technical Report No. 0944-27
"Comparison of the USP dissolution method and an alternate dissolution method for hydromorphone hydrochloride tablets USP, 8 mg"

Division's Response :

As far as possible, the firm should try to use the USP recommended analytical method. The provided analytical detection method for dissolution methodology is acceptable to the reviewer. The validation elements of the dissolution assay are given in Attachment I.

Division Deficiency :

The firm should provide % relative error or accuracy for the Benchtop and Freeze-thaw stability samples.

Firm's Response :

Enclosed in this part are tables of [redacted] stability data with percent relative error included.

Division Response :

The provided information is given in Attachment II. The [redacted] stability is acceptable.

RECOMMENDATIONS :

1. The firm has satisfactorily addressed the comments and deficiencies cited by the Division.

2. The bioequivalence study conducted by Roxane labs on its Hydromorphone HCl 8mg tablet, lot# 949053 comparing it to Knoll's Dilaudid, 8mg tablet, lot # 11200023 has been found acceptable by the Division of Bioequivalence. The study demonstrates that

Roxane's Hydromorphone HCl 8mg tablet is bioequivalent to the reference product, Dilaudid, 8mg tablet manufactured by Knoll.

3. The dissolution testing data conducted by Roxane labs on its Hydromorphone HCl 8mg tablet, lot # 949053 is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500ml of deaerated water at 37^0C using USP XXIII apparatus II (paddle) at 50rpm. The test product should meet the following specifications:

> Not less than 75% of the labelled amount of the drug in the dosage form is dissolved in 45 minutes.

4. From the bioequivalence point of view, the firm has met the requirements of in-vivo bioequivalence and in-vitro dissolution testing and the application is acceptable.

5. The new information about the half-life (around 30 hr instead of around 2 hr) should be referred to the labelling staff and the concerned medical officer.

/S/ 8/16/96

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD INITIALED BY YCHUANG /S/
FT INITIALED BY YCHUANG 8/19/96

Concur: /S/ Date: 8/27/96

Keith Chan, Ph.D.
Director, Division of Bioequivalence

(Sathe)

cc: ANDA # 74-597 (Original, Duplicate), Reviewer, HFD-652 (Huang), Drug File, Division File.

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Table D1. In Vitro Dissolution Testing

Drug (Generic Name): Hydromorphone Hydrochloride
Dose Strength: 8mg
ANDA No.: 74-597
Firm: Roxane Labs.
Submission Date: Dec.29, 1994

I. Conditions for Dissolution Testing:

USP XXIII Paddle RPM: 50
No. Units Tested: 12
Medium: Deaerated Water Volume: 500ml
Specifications: NLT 75% dissolved in 45min.
Reference Drug: Dilaudid Tablet by Knoll Labs.
Assay Methodology: [redacted]

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 949053 Strength (8.0mg)			Reference Product Lot # 11200023 Strength (8.0mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
15	72	[redacted]	16.7	47	[redacted]	6.4
30	93	[redacted]	6.1	66	[redacted]	5.9
45	100	[redacted]	1.6	89	[redacted]	4.5

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ON ORIGINAL

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Redacted 6

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OCT 19 1995

Hydromorphone Hydrochloride
8 mg Tablet
ANDA 74-597
Reviewer: Pradeep M. Sathe, Ph.D.
WP #74597SD.D94

Roxane Labs.
Columbus, Ohio-43216
Submission Date:
December 29, 1994

REVIEW OF A BIO-STUDY AND DISSOLUTION DATA

I.INTRODUCTION : Hydromorphone Hydrochloride is a hydrogenated ketone of morphine. It is a narcotic analgesic. It exerts primary effect on the central nervous system and organs containing smooth muscle. The drug is prescribed to the patients with acute or chronic pain.

The absorption of Hydromorphone HCl following oral administration is variable. Reports of oral availability of hydromorphone range from 20-50%. In normal volunteers, hydromorphone is metabolized primarily in the liver. It is excreted in the urine primarily as the glucuronide conjugate with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. As per the PDR 1995, "In a single crossover study in 27 normal subjects, the pharmacokinetics of 8 mg Dilaudid tablet was compared to 8 ml liquid (1mg/ml)". The plasma mean Cmax of the drug was 5.5 ng/ml, Tmax, 0.74 hr, AUC_{0-inf} 23.7 ng*hr/ml and $T_{1/2}$ 2.6 hr.

Currently, the reference, Knoll's Dilaudid is the only Hydromorphone Hydrochloride formulation on the market. The recommended dosing is 2 to 4 mg to be administered every 4 to 6 hr. Labelling does not state the drug administration in relation to food intake.

II.CURRENT SUBMISSION : The application consists of A] a single dose fasting bio-equivalency study comparing 8 mg test (Roxane) and reference (Knoll's Dilaudid^{R}) tablet formulations and B] dissolution testing methodology and data comparing the test and the reference formulations.

III.TEST FORMULATION : Following is the composition of the test formulation:

Ingredient	**Amount/Tablet**
Hydromorphone HCl (USP)	8.00mg
Lactose NF (Anhydrous)	[redacted]
Magnesium Stearate, NF	[redacted]
Total Weight	**150.0mg**

Hydromorphone HCl is the active ingredient, lactose is the [redacted] and magnesium stearate is the [redacted]

IV. STUDY PROTOCOL No. 210-06, [redacted] PROJECT No. 16409-1, BIOEQUIVALENCY STUDY :

A. TITLE : A bioequivalency study comparing two dosage forms of immediate release Hydromorphone HCl tablets, 8mg per tablet.

B. STUDY INVESTIGATORS AND CONTRACT LABORATORY :

1. Principal Investigator : [redacted] .

2. Bio-Study Site : [redacted]

3. Analytical Investigator : [redacted] .

C. STUDY OBJECTIVE : To evaluate the bioequivalency of a hydromorphone tablet, 8mg (Roxane) with a Dilaudid tablet, 8mg (Knoll Pharmaceuticals) using a two-period, crossover study design.

D. STUDY DESIGN AND NUMBER OF SUBJECTS : This was a single dose, fasted, randomized open label, two period, crossover study design with a 7-day washout period. Twenty-six healthy male subjects entered the study. A total of 25 subjects completed the study. Subject #3 was dropped from the study due to a positive urine drug screen at his period 2 check-in.

E. SUBJECT SELECTION/EXCLUSION CRITERIA : Volunteers were included in the study if they met the following:

1. Males between 19 and 50 years of age.

2. Body weight not more than 10% above or below the ideal weight for their height and frame.

3. No clinically significant findings on the physical examination.

4. Normal laboratory values unless the investigator considers the abnormality not clinically significant.

5. Negative urine screen for alcohol or drug abuse.

6. Voluntary consent to participate in the study

Volunteers were excluded from the study if they had the following:

1. History of alcohol or drug abuse at any time.

2. History of gastrointestinal tract, renal, hepatic, endocrine, oncologic or cardiovascular diseases or a history of tuberculosis, epilepsy, asthma, diabetes, psychosis or glaucoma.

3. History of allergic or adverse response to morphine or related

drugs. Subjects with a known hypersensitivity reaction to the following drugs (or products containing the following drugs) were excluded from the study: i) Codeine (Tylenol^{R} #2, #3, #4 and other generic brands), ii) Morphine (Oramorph SR^{R}, MS Contin^{R} and other generics), iii) Hydromorphone (Dilaudid^{R} and generics), Hydrocodone (Hycodan^{R} and generics), Levorphenol (Levo-Dremoran^{R} and generics), Oxycodone (Percocet^{R}, Percodan^{R}, Roxicet^{R}, Roxicodone^{R} and generics)

Subjects experiencing adverse effects such as (but not limited to) nausea, vomiting, lightheadedness were not considered to have an allergy to morphine derivated drugs. Only subjects with acute bronchospasm, anaphylaxis or hives secondary to one of the above agents were considered to have an allergy to morphine or morphine derivated drugs.

4. Participation in a previous clinical trial within the past 30 days.

5. Blood donation of one pint or more within the past 30 days.

6. Plasmapheresis within 7 days prior to study initiation.

7. Abnormal nutritional status. This includes "fad" and abnormal diets, excessive or unusual vitamin intakes, malabsorption (including gastrointestinal disease), psychological eating disorders, difficulty swallowing medication, significant recent weight change etc.

8. Treatment with any known enzyme inducing or altering agents (barbiturates, phenothiazines, cimetidine etc.) within the past 30 days.

9. Use of any prescription or over the counter medications on a regular basis.

F. SUBJECT RESTRICTIONS : The following restrictions were put on the subjects throughout the study:

1. No prescription medication for a period of at least 14 days prior to or during the study.

2. No over-the-counter (OTC) medication, including vitamins, analgesics, antacids etc. 72hr prior to or during each study period.

3. No alcoholic beverages 48hr prior to or during each study period.

4. No caffeine or xanthine-containing foods for 48hr prior to or during each study period.

G. STUDY SCHEDULES :

1. **Methods** : Each subject reported to the clinic on the evening prior to dose and received a snack at 20:00hr. The subjects were then required to fast for 10hr pre-dose and continued to fast for 4.5hr post-dose. Each individual was administered the test or reference formulation as per the randomization scheme. The dose was administered with 240ml tap water at room temperature. Standard lunch, dinner and snack was administered to each subject at 1130, 1730 and 2100hr.

2. **Randomization Schedule** :

Treatment Phase I	Phase II	Volunteer Number
A	B	2, 3, 5, 7, 11, 12, 13, 14, 18, 20, 21, 23, 25
B	A	1, 4, 6, 8, 9, 10, 15, 16, 17, 19, 22, 24, 26

3. **Blood Sampling** : Ten (10) ml samples were drawn into the heparinized vacutainer tubes at pre-dose (-1.0hr corresponding to 0hr), and 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, and 48.0hr post-dose. Thus, for each period the total blood draw was 15*10ml=150ml. After the blood sample collection, plasma samples were obtained by separation. The plasma samples were then stored at -20^{0}C until analysis.

H. DRUG TREATMENTS :

1. TEST PRODUCT A : Hydromorphone HCl Tablet, 8mg (Roxane Labs.), Lot #949053, Assay Potency= 98.4%, Batch Size= [redacted] units.

2. REFERENCE PRODUCT B : Dilaudid^{R} Tablet, 8mg (Knoll Pharmaceuticals), Lot #11200023, Assay Potency= 95.4%, Expiry date: April 1996.

I. ASSAY METHODOLOGY : **The following assay methodology may be a proprietary information of the firm and therefore should not be released under F.O.I.**

[redacted]

Analytical practice

Redacted _____ | _____

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J. PHARMACOKINETICS AND STATISTICS : The following pharmacokinetic parameters were evaluated for the assessment of bioequivalency: Cmax, the greatest observed plasma concentration, Tmax, the time of Cmax occurrence, AUC_t, area under the curve of the plasma concentration time profile up to the last measurable plasma concentration and AUC_{inf}, area under the curve of the plasma concentration time profile from time 0 to infinity. AUC_{inf} was calculated as $AUC_t + C_t/Kel$ where Kel is the elimination rate constant.

K. RESULTS OF THE BIOEQUIVALENCY STUDY : The mean plasma Hydromorphone concentration time levels for the test and the reference formulations are given in Table 1.1. The average pharmacokinetic parameters with the relevant statistics are given in tables 1.2 and 1.3. The mean plasma levels for the two treatments for up to 8hr and up to 48hr are given in Figures 1.4 and 1.5 respectively.

Table 1.1 : Hydromorphone HCl Mean plasma levels (ng/ml) with %CV values in the parentheses.

Time (hr)	Test (Roxane)	Ref. (Knoll)
-1.0 (0)	0.0 (---)	0.005 (500)
0.33	1.204 (75)	1.339 (109)
0.67	3.021 (41)	3.276 (44)
1.0	2.966 (33)	3.464 (35)
1.33	2.610 (31)	2.981 (36)
1.67	2.386 (35)	2.724 (32)
2.0	2.145 (31)	2.369 (32)
4.0	1.282 (30)	1.448 (35)
6.0	0.642 (34)	0.759 (34)
8.0	0.439 (42)	0.477 (34)
12.0	0.380 (37)	0.439 (27)
16.0	0.341 (37)	0.367 (33)
24.0	0.330 (29)	0.330 (26)
36.0	0.251 (32)	0.254 (34)
48.0	0.180 (55)	0.162 (42)

The table indicates that the mean test and the reference levels and the co-efficients of variation are comparable.

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Table 1.2: Mean Pharmacokinetic Parameters with respect to 48hr sampling

PK Parameter	Test (Roxane)	Reference (Knoll)	T/R ratio	90% Con.Int.
Cmax	3.525	3.951	0.892	82.4-96.0
Tmax	1.035	0.985	1.05	------
AUC	22.694	24.570	0.924	88.1-96.7
AUC_{inf}	31.630	32.575	0.97	85.0-109.2
$T_{1/2}$	30.4	30.8		-------
LCmax, Geom. Mean	1.207, 3.343	1.329, 3.777	0.88	81.0-96.8
LAUC, Geom.Mean	3.097, 22.1314	3.177, 23.974	0.92	87.9-96.9
$LAUC_{inf}$, Geom. Mean	3.397, 29.874	3.455, 31.658	0.94	85.3-104.4

Table 1.3: Mean Pharmacokinetic Parameters with respect to 8hr sampling

PK Parameter	Test (Roxane)	Reference (Knoll)	T/R Ratio	90% Con.Int.
Cmax	3.525	3.951	0.89	82.4-96.0
Tmax	1.035	0.985	1.05	--------
AUC	10.850	12.283	0.88	82.7-94.0
AUC_{inf}	12.540	14.173	0.88	83.3-93.7
$T_{1/2}$	2.503	2.608	0.96	-------
LCmax, Geom. Mean	1.207, 3.343	1.329, 3.777	0.88	81.0-96.8
LAUC, Geom. Mean	2.354, 10.527	2.474, 11.869	0.89	82.7-95.1
$LAUC_{inf}$, Geom. Mean	2.498, 12.158	2.615, 13.667	0.89	83.5-94.6

L. ADVERSE EFFECTS : Adverse effects were reported in 15 subjects. The severity of the adverse effects was mild to moderate. The

events included nausea, vomiting, tiredness, light-headedness, sleepiness, headache and diaphoretic. The adverse events were seen distributed more or less equally for the two treatments.

M. COMMENTS REGARDING THE BIOEQUIVALENCY STUDY :

1. A cursory examination of the results indicate that the mean test and the reference hydromorphone levels are comparable and so do their %CV. The individual plasma levels are comparable for the two formulations among different subjects. Undulating levels are seen for many subjects. This may be due to enterohepatic circulation. An intriguing feature of the plasma levels is that the zero time level was observed for subject #8 in the first period.

2. The mean pharmacokinetic parameters are also comparable and are within the limits of two one sided test suggesting bioequivalence of the two formulations.

3. It appears that the firm has calculated the AUC_{inf} based on the observed half-life (approximately 30hr) and the PDR reported half-life (approximately 2.5hr). The $AUC_{t(truncated)}/AUC_{inf}$ ratio for the set of data, which used 8hr as the truncation point, was more than 80%. The $AUC_{t(truncated)}/AUC_{inf}$ ratio for the set of data which used 48hr as the truncation point was more than only 70%. The average Cmax and Tmax values were comparable for both the formulations.

4. Based on the half-life of 30hr, the sampling scheme appears to be inadequate for a proper estimation of terminal rate constant and therefore AUC_{inf}. The question is however whether a firm could be held responsible for the increased assay sensitivity and consequently the changed half-life. The $AUC_{t(truncated)}/AUC_{inf}$ ratio for 48hr truncation was only more than 70% indicating inadequate duration of sampling. The individual plasma levels are however comparable for both formulations and even the mean pharmacokinetic parameters are within the limits of two one sided test suggesting a bioequivalence. The results are acceptable.

VI.DISSOLUTION METHODOLOGY : The following methodology was used for the comparative dissolution of the Roxane (test) and Knoll (reference) formulations.

Apparatus: USP XXIII Apparatus II (paddle)
Speed: 50rpm
Medium: Deaerated water
Volume: 500ml

The method is official in the USP.

A. RESULTS OF THE DISSOLUTION TESTING : The results are listed in Table D1.

B. COMMENTS ABOUT THE DISSOLUTION TESTING :

1. Even though the test formulation showed considerable variability at 15 minute sample point, the test and reference lot dissolutions are acceptable considering the USP Q limit.

2. It should be noted that the absorbance is measured at ——— instead of ——— as specified by the USP.

VII.OVERALL COMMENTS :

1. The study data raises some interesting questions as to a) what should be considered as true $T_{1/2}$ and b) if it is changed from the earlier reported value whether and how to modify the sampling scheme. It is important to note that the AUC_{inf} values would be substantially different if the observed Kel is different since AUC_{inf} calculation incorporates it.

2. On page 7 of original protocol, the sampling scheme is "(0)hr and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, and 24.0hr post-dose" which appears to be reasonable based on the PDR reported $T_{1/2}$. On page 2, the sampling scheme is modified as "(0)hr pre-dose and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0 and 48.0hr post-dose". If the $T_{1/2}$ is about 2hr, why the sampling scheme is extended up to 48hr? Was the firm aware of the longer $T_{1/2}$ due to increased assay sensitivity before the study started? If so why the sampling was not extended? Please respond.

3. It is surprising that Subject #8 showed hydromorphone levels at -1.0hr for the reference treatment. Is it due to the assay anomaly or due to subject non-compliance? Can it bias the analysis? Please respond.

4. The cross-reactivity of morphine is reported to be either ——— by the manufacturer or ——— by extrapolation. Please elaborate and clarify.

VIII.DEFICIENCIES :

1. The data should be reanalyzed excluding subject #8 who showed detectable levels in the first leg of the study.

2. Please explain why the dissolution absorbance is measured at ——— instead of ——— as stated in the USP.

3. The firm should provide % relative error or accuracy for the ——— stability samples.

IX.RECOMMENDATIONS :

1. The bioequivalence study conducted by Roxane labs on its Hydromorphone HCl 8mg tablet, lot# 949053 comparing it to Knoll's Dilaudid, 8mg tablet, lot # 11200023 has been found incomplete by the Division of Bioequivalence. The firm should submit additional information as requested in Deficiencies 1-3 and Overall Comments 2-4.

2. The dissolution testing data conducted by Roxane labs on its Hydromorphone HCl 8mg tablet, lot # 949053 is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500ml of deaerated water at 37°C using USP XXIII apparatus II (paddle) at 50rpm. The test product should meet the following specifications:

> Not less than 75% of the labelled amount of the drug in the dosage form is dissolved in 45 minutes.

3. If the observed half-life is believed to be around 30hr, the innovator and test formulation labelling will have to be modified to account for it. The new information labelling should be referred to the labelling staff and the concerned medical officer.

/S/

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD INITIALED BY YCHUANG
FT INITIALED BY YCHUANG /S/ 9/7/95

Concur: /S/ Date: 10/19/95
Keith Chan, Pn.D.
Director, Division of Bioequivalence

cc: ANDA # 74-597 (Original, Duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-652 (Huang, Sathe), Drug File, Division File.

Table D1. In Vitro Dissolution Testing

Drug (Generic Name): Hydromorphone Hydrochloride
Dose Strength: 8mg
ANDA No.: 74-597
Firm: Roxane Labs.
Submission Date: Dec.27, 1994

I. Conditions for Dissolution Testing:

USP XXIII Paddle RPM: 50
No. Units Tested: 12
Medium: Deaerated Water Volume: 500ml
Specifications: NLT 75% dissolved in 45min.
Reference Drug: Dilaudid Tablet by Knoll Labs.
Assay Methodology: ~~~

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 949053 Strength (8.0mg)			Reference Product Lot # 11200023 Strength (8.0mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
15	72	~~~	16.7	47	~~~	6.4
30	93	~~~	6.1	66	~~~	5.9
45	100	~~~	1.6	89	~~~	4.5

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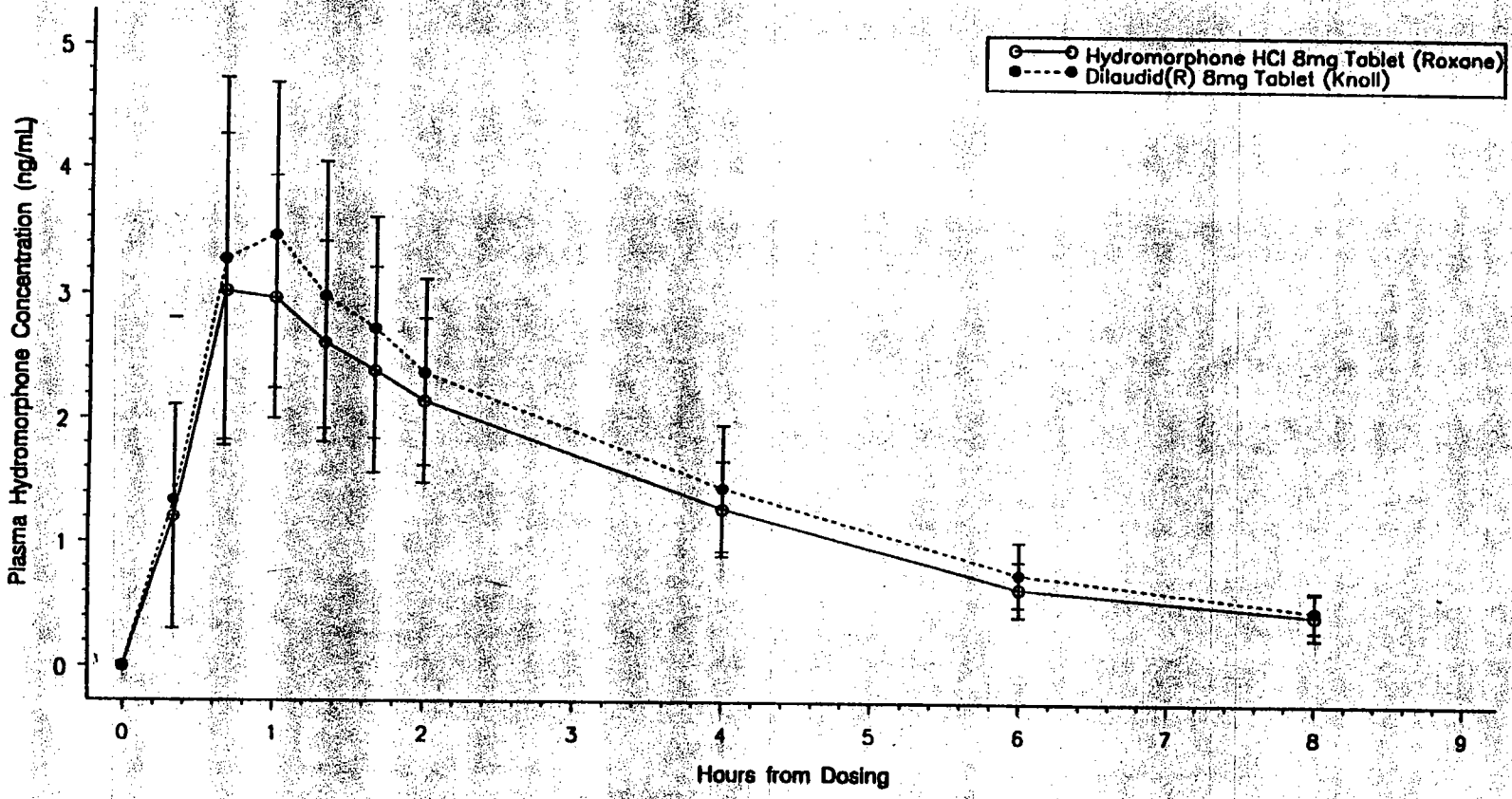
oxane Laboratories, Inc.
ydromorphone Protocol #210-06
arris Laboratories Project #16409

Figure 3

Mean (S.D.) Plasma Hydromorphone Concentrations Versus Time

0-8 hours - Linear Scale



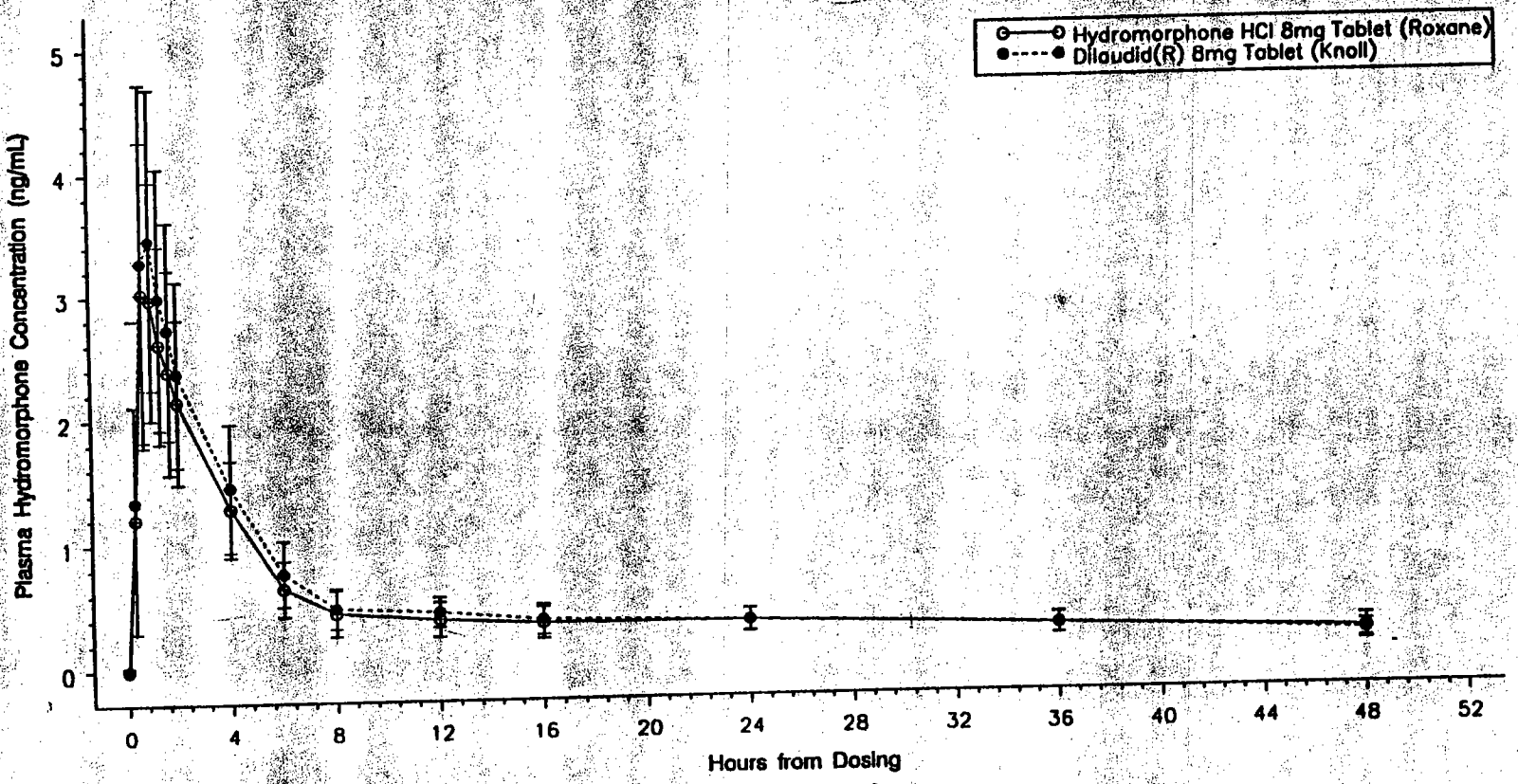
Attachment 1-4

Roxane Laboratories, Inc.
Hydromorphone Protocol #210-06
Harris Laboratories Project #16409

Figure 1

Mean (S.D.) Plasma Hydromorphone Concentrations Versus Time

0-48 hours - Linear Scale



Attachment 1.5

METHOD RESULTS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-597

ADMINISTRATIVE DOCUMENTS

Telephone Conversation Memorandum

ANDA: 74-597

DRUG: Hydromorphone Hydrochloride Tablets USP, 8 mg

FIRM: Roxane Laboratories, Inc.

PERSONS INVOLVED: Sean Alan F.X. Reade, Roxane
Tim Ames, FDA

PHONE NUMBER: 1800848-0120

DATE: 11/20/97

Called firm to inform them that the proposals submitted November 17, 1997 regarding the container/closure system (CCS) was unacceptable. I indicated that we needed to have the commitments and data to establish the product's stability and thereby allow for the 24 month expiration date. I indicated that I did not think this was a negotiable point and that we could not move toward approval without either stability data in the new CCS or the commitments plus post-approval submissions as outlined in the 11/6/97 teleconference. I indicated he could direct any further discussions about this issue to the Division of Chemistry II director, Dr. Frank Holcombe, if necessary. He indicated he'd get back to us after internal discussions.

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

/S/

cc: ANDA 74-597
Division file (1)
HFD-617/TAmes/PHONE.158
File: X:\new\firmsnz\roxane\telecons\phone.158

File ANDA 74-597

Telephone Conversation Memorandum

ANDA: 74-597

DRUG: Hydromorphone Hydrochloride Tablets USP, 8 mg

FIRM: Roxane Laboratories, Inc.

PERSONS INVOLVED: Sue Bastaja, Roxane
Tim Ames, FDA

PHONE NUMBER: 1800848-0120

DATE: 11/6/97

Called firm to request commitment regarding the new container/closure system for this product.

I explained that the recent request to withdraw the original container/closure system (CCS)(due to the discontinuation by the manufacturer) left the application without any stability data, as the firm had not submitted any stability data with the June 25, 1997 minor amendment. The firm acknowledged this point.

As a result I requested the firm provide the following:

1. A commitment (prior to the approval of the original ANDA) to demonstrate equivalency between the original CCS and the new CCS as a post-approval supplemental application filed as an Expedited Review Request, with the stipulation that the product would not be marketed until the supplemental application demonstrating the equivalency had been approved.

2. To provide (prior to the approval of the original ANDA) a protocol to be reviewed that would be used post-approval to demonstrate the equivalency between the two CCSs.

3. The protocol should include for the provision of accelerated stability data from one validation lot in the new CCS, and torque testing on both the application and removal of the closure done on the validation batch using the new CCS.

The firm was also given the option to provide this data (stability and torque testing) as an amendment to the unapproved original ANDA if they choose rather than providing it post approval.

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

/S/

cc: ANDA 74-597
Division file (1)
HFD-617/TAmes/PHONE.156
File: X:\new\firmsnz\roxane\telecons\phone.156

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-597

CORRESPONDENCE

Response to the Requests, continued:

Please note that Part C of the June 25, 1997 Minor Amendment response included Packaging Component Specifications, Certificates of Analysis, and moisture permeation data per USP 23 for the new bottle and closure. Also enclosed in Part C was a certification from the bottle manufacturer that all bottles meet the USP 23 specifications for Type III amber glass including the USP limits for ——— and the USP light transmission test.

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

Roxane Laboratories, Inc.

October 22, 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

FA

Re: ANDA 74-597
Hydromorphone Hydrochloride Tablets USP, 8 mg

NEW

FACSIMILE AMENDMENT

Dear Sir or Madame:

Reference is made to the above mentioned abbreviated new drug application, and to the facsimile amendment dated September 29, 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
B. Acknowledgments
C. Labeling 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,

Sue Bastaja for

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

RECEIVED
OCT 23 1997
GENERIC DRUGS

Enclosures

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

7/1/97
AM noted to
① Labeling Reviewer
② Chemistry Reviewer
for Review

Roxane Laboratories, Inc.

June 25, 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

Re: ANDA 74-597
Hydromorphone Hydrochloride Tablets USP, 8 mg

MINOR AMENDMENT

Dear Sir or Madame:

Reference is made to the above mentioned abbreviated new drug application, and to your correspondence dated July 25, 1996.

In response to the points raised in the correspondence, 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
B. Labeling Deficiencies
C. Addition of New Bottle and Closure
D. Addition of New Testing Facility

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.

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
JUN 27 1997
GENERIC DRUGS

Enclosure

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

ANDA 74-597

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

JUL 25 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated December 29, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydromorphone Hydrochloride Tablets USP, 8 mg.

Reference is also made to your amendment dated December 22, 1995.

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

A. Chemistry Deficiencies

1. Please provide the street address of the manufacturing site for the drug substance, Hydromorphone Hydrochloride for the purpose of inspection.

2. We note that Hydromorphone Hydrochloride is affected by light as per USP 23 and Remington's Pharmaceutical Sciences. Please include the operation procedures and precautions necessitated by the light sensitivity of the active ingredient.

3. A certification from ———— submitted in Part A.4.a. of your December 22, 1995 amendment is incomplete. Please submit available data for the amber glass bottle per USP 23.

4. Submit actual test results to demonstrate that the unit dose (blister) package meets the current USP 23 requirements for light-resistant containers.

5. Your assay test will not indicate whether Hydromorphone HCl has undergone ———— during the stability study. Please include a test and specification for the ———— of Hydromorphone Hydrochloride in the product release specifications and stability studies protocol.

B. Labeling Deficiencies

1. CONTAINER (100s) Satisfactory in draft.

2. UNIT DOSE BLISTER CARD Satisfactory in draft.

3. INSERT

a. We note that the NDC number on the 100s container label does not coincide with the NDC number as listed in the HOW SUPPLIED section. Please comment and/or revise.

b. We note that you have revised your draft insert labeling to include the information pertaining to the oral solution, which is the subject of ANDA 74-653. Please note, that if both applications are not approved at the same time, revisions may be needed prior to approval.

Please submit final printed labels and labeling.

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

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 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 **MINOR** amendment and should be so designated in your cover letter. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 7/24/96

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

Roxane Laboratories, Inc.

December 22, 1995

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 AMENDMENT
N/AC
RECEIVED
DEC 26 1995
GENERIC DRUGS

Re: NDA 74-597
Hydromorphone Hydrochloride Tablets USP, 8 mg

MAJOR AMENDMENT

Gentlemen:

Reference is made to the above mentioned new drug application, and to your correspondence dated June 26, 1995.

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

Part 1. Reference is made to your statement:

"1. Regarding components and composition:

a. The manufacturing site for the drug substance, Hydromorphone Hydrochloride USP, submitted on page 60 of the original submission is incorrect. Please provide the correct address of the manufacturing site for the drug substance.

b. Please submit the [redacted] of samples for ordinary impurities as tested by you and

c. Submit [redacted] analysis raw data for total unknown and total impurities from [redacted]

d. Submit additional tests which include [redacted] total unknown and total impurities from Roxane Laboratories, Inc."

Response:

a. The correct address of the manufacturing site for the drug substance is as follows:

[redacted]

Enclosed in this part are revised pages 60 and 115 of the original submission with the correct address.

/S/ 1-19-96

Response to Part 1 continued:

b. Enclosed in this part is a a revised Roxane Certificate of Analysis for Hydromorphone Hydrochloride USP, [redacted] Lot No. 3245 SLP064. A [redacted] for ordinary impurities, as tested by Roxane Laboratories is included as attachment 3. [redacted] does not retain [redacted], or [redacted] for lots of hydromorphone hydrochloride. Also enclosed is a letter containing [redacted] responses to the retention of [redacted]

c. [redacted] total unknown and total impurities are tested by [redacted] rather than [redacted] analysis raw data for total unknown and total impurities is consequently not available from [redacted] For you information, we have enclosed in this part [redacted] from [redacted] for a representative lot of Hydromorphone Hydrochloride USP ([redacted] Lot No. 3245 SLP058) tested for [redacted] total unknown and total impurities.

d. Enclosed in this part is a revised raw material specification from Roxane Laboratories. which includes an additional [redacted] test for [redacted], total unknown and total impurities. Enclosed in part A.1.b. is the revised certificate of analysis for Hydromorphone Hydrochloride USP, manufacturer's Lot No. 3245 SLP064, which includes results for [redacted], total unknown and total impurities. Also enclosed in this part is Technical Report 0944-31, "Verification of Chromatographic Purity for Hydromorphone Hydrochloride USP".

Part 2. Reference is made to your statement:

"2. Regarding excipients:

You are advised that microbiological testing should be conducted on each lot of components, prior to use in the manufacture of the drug product, for those components for which the microbial limits test is specified by USP/NF [21 CFR 211.84 (d) (6)]. Please provide a commitment to a 12-month retest period.

Response:

The two components used to manufacture the drug product, will be tested according to the official compendia, NF 18 and current supplement including microbial testing as required. Enclosed in this part are the updated raw material specifications to NF 18 and certificates of analysis for representative lots.

Roxane commits to retesting of stored raw materials requiring microbiological testing at least annually and those not requiring microbiological testing no less than every two years.

Redacted 9

Page(s) of trade secret and /or confidential commercial information

Response to Part 7:

a. Enclosed in this part is an updated stability report for Lot 949053, the unscored tablet configuration, which states the assay limits for Hydromorphone Hydrochloride as [redacted] Also enclosed in this part is a stability report for Lot 949086, the scored tablet configuration. The stability protocol has also been revised to include the assay limits for Hydromorphone HCl as [redacted] throughout the expiration period. The stability reports and stability protocol provide for room temperature storage conditions of 25 °C - 30 °C.

b. Our stability data report provides the percent of labeled amount dissolved in 45 minutes. The word [redacted] has been removed from the stability reports.

c. Please refer to our response for Part A.6.a. of this submission.

Part B. Labeling Deficiencies

Reference is made to your statement:

"1. Labeling:"

Response:

Enclosed in this part is the following draft labeling, revised as requested:

b. Unit dose blister card
a. Bottles of 100 tablets
c. Package outsert

Hydromorphone Hydrochloride
ANDA 74-597

NOV 14 1995

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

Dear Mr. Chmielewski:

Reference is made to the *in vivo* bioequivalence data submitted on December 29, 1994, for Hydromorphone Hydrochloride Tablets USP, 8 mg.

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

1. The original protocol (Page 7), specified that, the sampling scheme is "(0)hr, and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, and 24.0hr post-dose" which appears to be reasonable based on the PDR-95 reported $T_{1/2}$. On page 2, the sampling scheme is modified to "(0)hr pre-dose, and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0 and 48.0hr post-dose". If the $T_{1/2}$ is about 2hr, why was the sampling scheme extended up to 48hr? Were you aware of the longer $T_{1/2}$ before the study started? If not, why was the sampling extended? Please respond.

3. Subject #8 showed hydromorphone levels at -1.0 hr for the reference treatment. Was it due to an assay anomaly, or to subject non-compliance? Can it bias the analysis? Please comment. The data should be reanalyzed excluding subject #8 who showed detectable levels in the first leg of the study.

4. The cross-reactivity of morphine is reported to be either ——— by the manufacturer or ——— by extrapolation. Please elaborate and clarify.

5. Please explain why the dissolution absorbance is measured at ——— instead of ———

6. Provide percent relative error or accuracy for the ——— and ——— stability samples.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment should respond to all comments contained in this correspondence. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

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

2-1

ANDA 74-597

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

SEP - 3 1996

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 Hydromorpone Hydrochloride Tablets USP, 8 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/

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

ANDA 74-597

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

JUN 26 1995

Dear Madam:

This is in reference to your abbreviated new drug application dated December 29, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydromorphone Hydrochloride Tablets USP, 8 mg.

Reference is also made to your amendment dated January 26, 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:

a. The manufacturing site for the drug substance, Hydromorphone Hydrochloride USP, submitted on page 60 of the original submission is incorrect. Please provide the correct address of the manufacturing site for the drug substance.

b. Please submit the ——— of samples for ordinary impurities as tested by you and ———

c. Submit — analysis raw data for total unknown and total impurities from ———

d. Submit additional tests which include ——— total unknown and total impurities from Roxane Laboratories, Inc.

2. Regarding excipients:

You are advised that microbiological testing should be conducted on each lot of components, prior to use in the manufacture of the drug product, for those components for which the

microbial limits test is specified by USP/NF [21 CFR 211.84 (d) (6)]. Please provide a commitment to a 12-month retest period.

3. The submission fails to provide a complete formula card and satisfactory batch records. In this regard:

a. [redacted]

b. [redacted] parameters should be included.

c. Submit blank packaging control sheets or packaging records including label and insert controls.

d. The batch record should indicate at what point the blend is taken for analysis and the result should be recorded on the completed batch record.

e. Submit the specifications and assay test results for the active ingredients from top, middle and bottom during in-process [redacted] test prior to [redacted]

f. We note that in-process testing documentation was provided. Please provide the acceptable limits for those tests, also include the assay test for Hydromorphone Hydrochloride and submit the revised in-process testing specifications.

g. The specifications for the active ingredient (e.g., [redacted] of top, middle and bottom portions), in-process controls, and a blank release certificate with methods and specifications should be included in blank commercial production lot batch records. Please submit the blank batch records for the [redacted] tablet production run.

h. Include the operation procedures and precautions necessitated by the light sensitivity and control status of the active ingredient.

4. Your application fails to present complete descriptions of the container/closure systems. In that regard:

   a. How do you determine whether the Amber glass is Type III?

   b. Please submit manufacturer's COA or your COA for the amber glass bottle per USP 23.

   c. Submit a sampling plan and acceptance specifications for containers.

   d. Submit the following information for the unit dose (blister) package:

      i. Please identify the manufacturer, supplier, and composition for each component of the unit dose system (blister package) in tabulated form.

      ii. Physical characteristics (size, dimension, construction, etc) and engineering diagrams.

      iii. Light transmission test.

      iv. Physico-chemical tests.

      v. Acceptance specifications.

5. The submission fails to include satisfactory packaging records. In this regard:

   a. Provide a detailed description of the packaging and labeling procedures for the drug product.

   b. Include a summary of your label accountability procedures.

6. Regarding finished product:

   a. Please include in your COA, test(s) and specification(s) for the optical purity of the active ingredient in the product.

   b. We note the alternate — assay procedure for Hydromorphone Hydrochloride Tablets USP, 8 mg, was used for the scored dosage form (see page 303). In this regard, it should be understood that the official compendium

procedures will be employed for regulatory purposes in case of any dispute. No data was presented to demonstrate that the —— method is equivalent to the USP method. Please submit available comparison data.

c. We note the alternate dissolution method for Hydromorphone Hydrochloride Tablets USP, 8 mg, was used for the dosage form. Please clarify.

d. We note an alternate method for the Uniformity of Dosage Units was used for the scored dosage form (see page 303). Please clarify.

e. Submit sample chromatograms to document that the excipients do not interfere with Hydromorphone Hydrochloride assay in the finished product.

f. Please provide an adequate stability-indicating assay method. In this regard:

i) Present, in percentages the assay values of the active ingredient and degradation products under various stress conditions in tabular form.

ii) Your validated stability indicating —— method has not been shown to be an ———— method. Hence, an assay test will not indicate whether Hydromorphone HCl has undergone ———— during the stability study. ———— would be the simplest test to ascertain that the product has not undergone ———— Please submit a test and any available data.

g. Please submit revised product release certificate including a test for ———— of active in product.

7. Your application fails to contain a satisfactory stability protocol and stability data. In this regard:

a. Specification for Hydromorphone HCl must be indicate actual number rather than stated as "± 10%" in the stability data report.

b. We note in your stability data report (see pages 567-569) you refer to "dissolution rate" testing. Please clarify your specifications. Is rate testing actually employed.

c. It should be demonstrated that the ——— purity of active remains the acceptable through the shelf-life of the product.

B. Labeling Deficiencies

CONTAINER: 100's

a. Revise your storage recommendations to be the same as the listed drug:

Store between 15° - 25°C (59° - 77°F)

b. ' ——————— - Please comment on the need for this statement or delete.

c. What is the purpose of the statement ' ——— ——————" on a container with CRC?

d. "Usual Dosage: See Package ...".

UNIT DOSE BLISTER CARD: 25's

a. See comments a., b., and d. under CONTAINER.

b. Remove ' ——— from the boxed area, as seen on your container labels.

c. We note that you have proposed packaging this light-sensitive drug in a non-light-resistant package. The listed drug is packaged with light-resistant materials. Please comment. If light resistant materials are not used, it is necessary to include the phrase "Protect from light".

UNIT DOSE BLISTER LABEL:

Satisfactory, in draft.

INSERT:

1. GENERAL COMMENT

   Subsection headings should be less prominent than section headings and should be of equal prominence to each other throughout the text.

2. DESCRIPTION

   a. Include the molecular formula.

   b. Include the chemical name.

   c. To be in accord with USP 23, revise the molecular weight to read 321.81.

   d. Revise the last paragraph to read:

      Each tablet, for oral administration, contains 8 mg of hydromorphone hydrochloride. In addition, each tablet contains the following inactive ingredients...

3. CLINICAL PHARMACOLOGY

   a. First paragraph

      Delete ' _____ 2 instances)

   b. Eighth paragraph, last line - ... and red eyes.

   c. Ninth paragraph - ... any ... (spelling)

   d. Pharmacokinetics

      i. Revise the first paragraph to read as follows:

         The pharmacokinetic parameters from a reported single-dose crossover study of 27 normal subjects are outlined below. Plasma hydromorphone concentration was determined using a sensitive and specific assay.

      ii. Delete the information in the table relating to the oral liquid.

e. Clinical Trials

i. Delete [redacted] (4 instances)

ii. Third line

... studied ... (spelling)

iii. sixth line

...another trial... (insert space)

f. Individualization of Dosage

i. Delete the word " [redacted] throughout this subsection. (5 instances)

ii. Second paragraph, second line.

... 2 to 4 mg ...

iii. Delete the proprietary names from the table.

iv. Delete the terminal zeros in 2 mg and 1 mg from the table.

g. We reserve final comment on this section until we have reviewed your bioequivalency studies.

4. WARNINGS

Delete "[redacted]". (6 instances)

5. PRECAUTIONS

a. Delete '[redacted] throughout this section.

b. Use in Biliary Surgery

... about to undergo ...

c. *Pregnancy - Pregnancy Category C*

Retitle this subsection as follows:

Pregnancy: Teratogenic Effects:
Pregnancy Category C:

d. Pediatric Use

... in pediatric patients have not ...

e. Geriatric Use

...has not been...

6. ADVERSE REACTIONS

Second paragraph, fifth line

... and in ...

7. DRUG ABUSE AND DEPENDENCE

a. Delete ~~———~~ throughout this section except in the first sentence.

b. Last paragraph, first line

... dependence on ... (rather than "~~———~~

8. OVERDOSAGE

a. Delete ~~———~~ throughout this section except in the first sentence.

b. Non-Tolerant Patient, paragraph 1.

i. Fourth line

...naloxone hydrochloride...

ii. Delete the terminal zero in 2 mg.

9. DOSAGE AND ADMINISTRATION

a. Revise the first paragraph to read:

The usual starting dose for hydromorphone hydrochloride tablets is ...

b. Second paragraph, second line

... is inadequate ...

c. Safety and Handling Instructions

Revise the second sentence to read as follows:

Significant absorption from dermal exposure is unlikely.

10. HOW SUPPLIED

a. Add the statement "Protect from light" to this section.

b. Change the storage recommendations to be in accord with those of the listed drug.

Revise your insert labeling, then prepare and submit final printed container and unit dose labels and draft insert labeling.

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 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. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 4/26/95

Florence S. Fang
Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-597

Roxane Laboratories, Inc.
Attention: Sue T. Bastaja
P.O. Box 16532
Columbus, OH 43216-6532

MAR 8 1995

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated January 20, 1995, and your amendment dated January 26, 1995.

NAME OF DRUG: Hydromorphone Hydrochloride Tablets USP, 8 mg

DATE OF APPLICATION: December 29, 1994

DATE OF RECEIPT: December 30, 1994

DATE ACCEPTABLE FOR FILING: January 27, 1995

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

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Timothy Ames
Consumer Safety Officer
(301) 594-0305

Sincerely yours,

|S| 3/8/95

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

ANDA 74-597
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Acting Chief |S| 2/22/95 date
HFD-615/WRussell, CSO |S| 2/2/95 date
HFD-647/JSimmons, Sup Chemist |S| 2.27.95 date
HFD-610/JPhillips, Chief LRB |S| 2/27/95 date
WP File\russell\74\74-597
F/T bcw/2-2-95
ANDA Acknowledgement Letter! |S|

ANDA 74-597

Roxane Laboratories, Inc.
Attention: Sue T. Bastaja
P.O. Box 16532
Columbus, OH 43216-6532

JAN 20 1995

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated December 29, 1994, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydromorphone Hydrochloride Tablets USP, 8 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> You have failed to provide a patent certification as required by the Federal Food, Drug, and Cosmetic Act, Section 505(j)(2)(A)(vii), [21 CFR 314.94(a)(12)].

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, while you did provide side-by-side copies of your proposed labeling and the reference listed drug, you made no effort to annotate and explain any differences. Please provide a side-by-side comparison of your proposed labeling with the approved labeling for the reference listed drug with all differences **annotated and explained** [314.94(a)(8)(iv)].

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/ 1/20/95

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

ANDA 74-597
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Acting /S/ 1/16/95 date
HFD-615/WRussell, CSO /S/ 1/18/95 date
HFD-610/JPhillips, Chief, LRB /S/ date 1/17/95
HFD-647/Chem Branch /S/ date 1/18/95
WP File\russell\74\74-597
F/T bcw/1-11-95
ANDA Refuse to File!