

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

Approval Package for:

APPLICATION NUMBER:

70-189

Generic Name: Naloxone Hydrochloride Injection, USP,
0.02mg/mL, 2mL Tubex

Sponsor: Wyeth Laboratories

Approval Date: October 2, 1985

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

70-189

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	X
Medical Officer Review(s)	
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

70-189

APPROVAL LETTER

ANDA 70-189

Wyeth Laboratories
Attention: Joseph N. Bathish
Post Office Box 8295
Philadelphia, Pennsylvania 19101

OCT 2 1985

Dear Mr. Bathish:

Reference is made to your abbreviated new drug application dated December 28, 1984, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Maloxone Hydrochloride Injection, USP, 0.02 mg/ml, 2 ml Tubex.

Reference is made to your communication dated September 17, and August 12, 1985.

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; however, the effective date of approval is delayed until September 24, 1986 pursuant to 21 U.S.C. 355 (j)(4)(D) relating to market exclusivity. This Division should be advised of any change in the marketing status of this drug. Invs, if circumstances arise which may have impact upon the effective date of approval (e.g. a license agreement between you and the patent holder), you are requested to supplement your application with documentation from the patent holder that a licensing agreement exists and include any relevant conditions or restrictions.

Any significant change in the conditions outlined in this abbreviated application requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.6 of the New Drug Regulations.

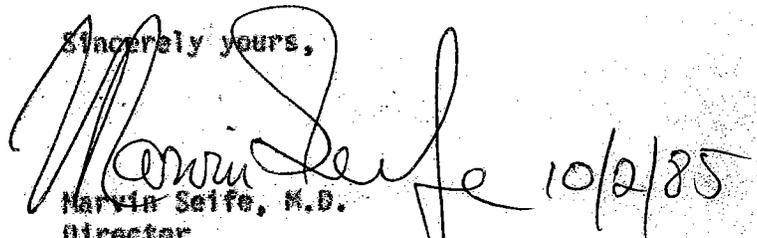
Postmarketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80 and 314.81.

For Initial Campaigns: At or near the effective date of approval, we request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your immediate 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 Advertising and Labeling (HFN-240). Please do not use Form FD-2263 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

For Subsequent Campaigns: We call your attention to Section 314.81(b)(3) of the Regulations which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Advertising and Labeling (HFN-240) with a completed Form FD-2253.

The introduction or delivery for introduction into interstate commerce of the drug before the effective approval date is prohibited under 21 U.S.C. 331(d).

Sincerely yours,



Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

PHI-DO

HFN-83

HFN-230

RBrown/JMeyer/BHO

R/D INITIALED BY: JMeyer/MSeife

D Utz: 9-30-85 (0903R)

APPROVAL

RSB
9/30/85

BH
JMeyer 10/2/85

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

70-189

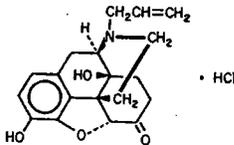
FINAL PRINTED LABELING

Wyeth® Naloxone HCl Injection, USP

Naloxone HCl Injection, USP *BOT* (Pediatric)

Description

Naloxone hydrochloride, a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group. Naloxone hydrochloride is designated chemically as 17-allyl-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one hydrochloride with the following chemical structure:



Naloxone hydrochloride occurs as a white to slightly off-white powder. It is soluble in water, in diluted acids, and in strong alkali. It is slightly soluble in alcohol and practically insoluble in ether and in chloroform.

Each mL of sterile injection contains either 0.02 mg or 0.4 mg of naloxone hydrochloride; 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben, as preservatives, in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

Clinical Pharmacology

Naloxone hydrochloride is essentially a pure narcotic antagonist; i.e., it does not possess the "agonistic" or morphinelike properties characteristic of other narcotic antagonists. It prevents or reverses the effects of opioids, including respiratory depression, sedation, and hypotension. Also, it can reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine. Naloxone does not produce respiratory depression, psychotomimetic effects, or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists, it exhibits essentially no pharmacologic activity.

Naloxone hydrochloride has not been shown to produce tolerance or to cause physical or psychological dependence.

In the presence of physical dependence on narcotics, naloxone hydrochloride will produce withdrawal symptoms.

While the mechanism of action of naloxone hydrochloride is not fully understood, the preponderance of evidence suggests that it antagonizes the opioid effects by competing for the same receptor sites.

When given intravenously, the onset of action of naloxone hydrochloride is generally within two minutes; it is slightly less rapid when the drug is administered intramuscularly or subcutaneously. The duration of action is dependent upon the dose and route of administration—intramuscular administration produces a more prolonged effect than the intravenous one. The requirement for additional doses of naloxone hydrochloride, however, will also be dependent upon the amount, type, and route of administration of the narcotic being antagonized.

Naloxone hydrochloride, given parenterally, is rapidly distributed in the body. It is metabolized in the liver, primarily by glucuronide conjugation, and is excreted in the urine. The serum half-life in a study in adults ranged from 30 to 81 minutes (mean 64 \pm 12 minutes). In a neonatal study the mean plasma half-life was observed to be 3.1 \pm 0.5 hours.

Indication and Usage

Naloxone hydrochloride is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by opioids, including natural and synthetic narcotics, propoxyphene, methadone, and the narcotic-antagonist analgesics: nalbuphine, pentazocine, and butorphanol. It is also indicated for the diagnosis of suspected acute opioid overdosage.

Contraindications

Naloxone hydrochloride is contraindicated in patients known to be hypersensitive to it.

Warnings

Naloxone hydrochloride should be administered with caution to persons (including newborns of dependent mothers) who are known or suspected to be physically dependent on opioids. In such cases abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

Patients who appear to have satisfactorily responded to naloxone hydrochloride should be kept under continuous surveillance, and additional doses of naloxone hydrochloride should be given, as necessary, since the duration of action of some narcotics may exceed that of naloxone.

Naloxone hydrochloride is not effective against respiratory depression due to nonopioid drugs.

Precautions

In addition to naloxone hydrochloride, other resuscitative measures, such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents, should be available and employed, when necessary, to counteract acute narcotic poisoning.

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been reported. These have occurred in postoperative patients, most of whom had preexisting cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause-and-effect relationship has not been established, naloxone hydrochloride should be used with caution in patients with preexisting cardiac disease or in patients who have received potentially cardiotoxic drugs.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenicity and mutagenicity studies have not been performed with naloxone hydrochloride. Reproductive studies in rats and mice demonstrated no impairment of fertility.

PREGNANCY

Teratogenic Effects—Pregnancy Category B

Reproduction studies performed in rats and mice at doses of naloxone hydrochloride up to 1,000 times the human dose revealed no evidence of impaired fertility or harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naloxone hydrochloride should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether naloxone hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when naloxone hydrochloride is administered to a nursing woman.

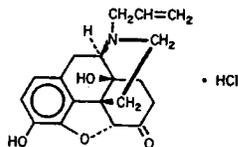
Adverse Reactions

Abrupt reversal of narcotic depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, and tremulousness. In postoperative patients, larger than necessary dosage of naloxone hydrochloride may result in significant reversal of analgesia and in excitement. Hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been associated with the use of naloxone hydrochloride postoperatively (see "Precautions and Dosage and Administration—Usage in Adults—Postoperative Narcotic Depression"). Seizures have been reported to occur infrequently after the administration of naloxone hydrochloride.

PROVED

OCT 2 1985

the nitrogen atom is replaced by an allyl group. Naloxone hydrochloride is designated chemically as 17-allyl-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one hydrochloride with the following chemical structure:



Naloxone hydrochloride occurs as a white to slightly off-white powder. It is soluble in water, in diluted acids, and in strong alkali. It is slightly soluble in alcohol and practically insoluble in ether and in chloroform.

Each mL of sterile injection contains either 0.02 mg or 0.4 mg of naloxone hydrochloride; 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben, as preservatives, in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

Clinical Pharmacology

Naloxone hydrochloride is essentially a pure narcotic antagonist; i.e., it does not possess the "agonistic" or morphinelike properties characteristic of other narcotic antagonists. It prevents or reverses the effects of opioids, including respiratory depression, sedation, and hypotension. Also, it can reverse the psychomimetic and dysphoric effects of agonist-antagonists such as pentazocine. Naloxone does not produce respiratory depression, psychomimetic effects, or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists, it exhibits essentially no pharmacologic activity.

Naloxone hydrochloride has not been shown to produce tolerance or to cause physical or psychological dependence.

In the presence of physical dependence on narcotics, naloxone hydrochloride will produce withdrawal symptoms.

While the mechanism of action of naloxone hydrochloride is not fully understood, the preponderance of evidence suggests that it antagonizes the opioid effects by competing for the same receptor sites.

When given intravenously, the onset of action of naloxone hydrochloride is generally within two minutes; it is slightly less rapid when the drug is administered intramuscularly or subcutaneously. The duration of action is dependent upon the dose and route of administration—intramuscular administration produces a more prolonged effect than the intravenous one. The requirement for additional doses of naloxone hydrochloride, however, will also be dependent upon the amount, type, and route of administration of the narcotic being antagonized.

Naloxone hydrochloride, given parenterally, is rapidly distributed in the body. It is metabolized in the liver, primarily by glucuronide conjugation, and is excreted in the urine. The serum half-life in a study in adults ranged from 30 to 81 minutes (mean 64 \pm 12 minutes). In a neonatal study the mean plasma half-life was observed to be 3.1 \pm 0.5 hours.

Indication and Usage

Naloxone hydrochloride is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by opioids, including natural and synthetic narcotics, propoxyphene, methadone, and the narcotic-antagonist analgesics: nalbuphine, pentazocine, and butorphanol. It is also indicated for the diagnosis of suspected acute opioid overdosage.

Contraindications

Naloxone hydrochloride is contraindicated in patients known to be hypersensitive to it.

Warnings

Naloxone hydrochloride should be administered with caution to persons (including newborns of dependent mothers) who are known or suspected to be physically dependent on opioids. In such cases abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

Patients who appear to have satisfactorily responded to naloxone hydrochloride should be kept under continuous surveillance, and additional doses of naloxone hydrochloride should be given, as necessary, since the duration of action of some narcotics may exceed that of naloxone.

Naloxone hydrochloride is not effective against respiratory depression due to nonopioid drugs.

Precautions

In addition to naloxone hydrochloride, other resuscitative measures, such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents, should be available and employed, when necessary, to counteract acute narcotic poisoning.

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been reported. These have occurred in postoperative patients, most of whom had preexisting cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause-and-effect relationship has not been established, naloxone hydrochloride should be used with caution in patients with preexisting cardiac disease or in patients who have received potentially cardiotoxic drugs.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenicity and mutagenicity studies have not been performed with naloxone hydrochloride. Reproductive studies in rats and mice demonstrated no impairment of fertility.

PREGNANCY

Teratogenic Effects—Pregnancy Category B

Reproduction studies performed in rats and mice at doses of naloxone hydrochloride up to 1,000 times the human dose revealed no evidence of impaired fertility or harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naloxone hydrochloride should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether naloxone hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when naloxone hydrochloride is administered to a nursing woman.

Adverse Reactions

Abrupt reversal of narcotic depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, and tremulousness. In postoperative patients, larger than necessary dosage of naloxone hydrochloride may result in significant reversal of analgesia and in excitement. Hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been associated with the use of naloxone hydrochloride postoperatively (see "Precautions" and "Dosage and Administration—Usage in Adults—Postoperative Narcotic Depression"). Seizures have been reported to occur infrequently after the administration of naloxone; however, a causal relationship has not been established.

Overdosage

There is no clinical experience with naloxone hydrochloride overdosage in humans. In the mouse and the rat, the intravenous LD₅₀ is 150 \pm 5 mg/kg and 109 \pm 4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats, the LD₅₀ (95% CL) is 260 (228 to 296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for three weeks produced only transient salivation and partial ptosis. No toxic effects were seen at 10 mg/kg/day for three weeks.

Dosage and Administration

Naloxone hydrochloride may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved with the intravenous route; this route is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of naloxone hydrochloride, patients should be kept under continued surveillance, and additional doses of naloxone hydrochloride should be administered as necessary.

INTRAVENOUS INFUSION

For administration via intravenous infusion, naloxone hydrochloride may be diluted in normal saline or 5% dextrose solutions. The addition of 2 mg of naloxone hydrochloride to 500 mL of solution provides a concentration of 0.004 mg/mL. A mixture of either solution should be used within 24 hours. After 24 hours, the remaining unused solution must be discarded. The rate of administration should be titrated in accordance with the patient's response.

Naloxone hydrochloride should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high molecular weight anions, or any solution having an alkaline pH. No drug or chemical agent should be added to naloxone hydrochloride unless its effect on the chemical and physical stability of the solution has first been established.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

USAGE IN ADULTS

Narcotic Overdose—Known or Suspected

An initial dose of 0.4 mg to 2.0 mg of naloxone hydrochloride may be given intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, the dose may be repeated at two- to three-minute intervals. If no response is observed after 10 mg of naloxone hydrochloride, the diagnosis of narcotic-induced or partial-narcotic-induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Postoperative Narcotic Depression

For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of naloxone hydrochloride are usually sufficient. The dose of naloxone should be titrated according to the patient's response. For the initial reversal of respiratory depression, naloxone hydrochloride should be injected in increments of 0.1 to 0.2 mg intravenously at two- to three-minute intervals to the desired degree of reversal, i.e., adequate ventilation and alertness without significant pain or discomfort. Larger than necessary dosage of naloxone hydrochloride may result in significant reversal of analgesia and increase in blood pressure. Similarly, too-rapid reversal may induce nausea, vomiting, sweating, or circulatory stress.

Additional doses of naloxone hydrochloride may be required within one- to two-hour intervals depending upon the amount, type (i.e., short- or long-acting narcotic), and time interval since its last administration. Supplemental intramuscular doses of naloxone have been shown to produce a longer-lasting effect.

USAGE IN CHILDREN

Narcotic Overdose—Known or Suspected

The usual initial dose in children is 0.01 mg/kg body weight given intravenously. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an intravenous route of administration is not available, naloxone hydrochloride may be administered intramuscularly or subcutaneously in divided doses. If necessary, naloxone hydrochloride can be diluted with sterile water for injection.

Postoperative Narcotic Depression

Follow the recommendations and cautions under "Adult Postoperative Narcotic Depression." For the initial reversal of respiratory depression, naloxone hydrochloride should be injected in increments of 0.005 mg to 0.01 mg intravenously at two- to three-minute intervals to desired degree of reversal.

USAGE IN NEONATES

Narcotic-Induced Depression

The usual initial dose is 0.01 mg/kg body weight administered intravenously, intramuscularly, or subcutaneously. This dose may be repeated in accordance with adult administration guidelines for the initial reversal of respiratory depression, as provided in the section on "Postoperative Narcotic Depression."

How Supplied

Naloxone HCl Injection, USP, Wyeth®, is available in vials and in TUBEX® Sterile Cartridge-Needle Units in the following dosage strengths:

0.02 mg per mL (Pediatric)

NDC 0008-0688-01, 2 mL vial, in packages of 10 vials.

NDC 0008-0688-02, 2 mL TUBEX (25 gauge x 5/8 inch needle), in packages of 10 TUBEX.

0.4 mg per mL

NDC 0008-0689-01, 1 mL vial, in packages of 10 vials.

NDC 0008-0689-02, 1 mL TUBEX (25 gauge x 5/8 inch needle), in packages of 10 TUBEX.

NDC 0008-0689-03, 10 mL vial, individually boxed.

NDC 0008-0689-04, 1 mL TUBEX (22 gauge x 1¼ inch needle), in packages of 10 TUBEX.

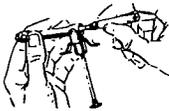
Protect from light

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

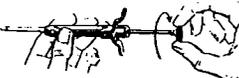
Directions for use of TUBEX® SYRINGE QUICK-LOADING 1 AND 2 ML SIZE To load the TUBEX Hypodermic Syringe



1. Grasp barrel of syringe in one hand. With the other hand, pull back firmly on plunger and swing the entire handle-section downward so that it locks at right angle to the barrel.



2. Insert TUBEX Sterile Cartridge-Needle Unit, needle end first, into the barrel. Engage needle ferrule by rotating it clockwise in the threads at front end of syringe.



3. Swing plunger back into place and attach end to the threaded shaft of the piston. Hold the syringe barrel with one hand and rotate plunger until both ends of TUBEX Sterile Cartridge-Needle Unit are fully, but lightly, engaged. To maintain sterility, leave the rubber sheath in place

To remove the empty TUBEX



Replace sheath with a twisting motion to prevent needle from snagging. Disengage plunger from piston by rotating counter-clockwise, and open syringe as in step No. 1. Do not pull plunger back before disengaging or syringe will jam. Rotate TUBEX Cartridge-Needle Unit counter-clockwise to disengage at front end of syringe, remove from syringe and discard.

To adapt 2 mL syringe to 1 mL TUBEX



The 2 mL syringe can be used for a 1 mL TUBEX. Engage both ends of TUBEX and push the slide through so the number "1" appears. After use, the syringe automatically resets itself for 2 mL TUBEX.

NOTE: Any graduated markings on TUBEX Sterile Cartridge-Needle Units are to be used as a guide in aspirating or administering measured doses.

Used TUBEX Cartridge-Needle Units should not be employed for successive injections or as multiple-dose containers. They are intended to be used only once and discarded. (Refer to discarding the sheath.)

tioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

Postoperative Narcotic Depression

For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of naloxone hydrochloride are usually sufficient. The dose of naloxone should be titrated according to the patient's response. For the initial reversal of respiratory depression, naloxone hydrochloride should be injected in increments of 0.1 to 0.2 mg intravenously at two- to three-minute intervals to the desired degree of reversal, i.e., adequate ventilation and alertness without significant pain or discomfort. Larger than necessary dosage of naloxone hydrochloride may result in significant reversal of analgesia and increase in blood pressure. Similarly, too-rapid reversal may induce nausea, vomiting, sweating, or circulatory stress. Additional doses of naloxone hydrochloride may be required within one- to two-hour intervals depending upon the amount, type (i.e., short- or long-acting narcotic), and time interval since its last administration. Supplemental intramuscular doses of naloxone have been shown to produce a longer-lasting effect.

USAGE IN CHILDREN

Narcotic Overdose—Known or Suspected

The usual initial dose in children is 0.01 mg/kg body weight given intravenously. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an intravenous route of administration is not available, naloxone hydrochloride may be administered intramuscularly or subcutaneously in divided doses. If necessary, naloxone hydrochloride can be diluted with sterile water for injection.

Postoperative Narcotic Depression

Follow the recommendations and cautions under "Adult Postoperative Narcotic Depression." For the initial reversal of respiratory depression, naloxone hydrochloride should be injected in increments of 0.005 mg to 0.01 mg intravenously at two- to three-minute intervals to desired degree of reversal.

USAGE IN NEONATES

Narcotic-Induced Depression

The usual initial dose is 0.01 mg/kg body weight administered intravenously, intramuscularly, or subcutaneously. This dose may be repeated in accordance with adult administration guidelines for the initial reversal of respiratory depression, as provided in the section on "Postoperative Narcotic Depression."

How Supplied

Naloxone HCl Injection, USP, Wyeth®, is available in vials and in TUBEX® Sterile Cartridge-Needle Units in the following dosage strengths:

0.02 mg per mL (Pediatric)

NDC 0008-0688-01, 2 mL vial, in packages of 10 vials.

NDC 0008-0688-02, 2 mL TUBEX (25 gauge x 5/8 inch needle), in packages of 10 TUBEX.

0.4 mg per mL

NDC 0008-0689-01, 1 mL vial, in packages of 10 vials.

NDC 0008-0689-02, 1 mL TUBEX (25 gauge x 5/8 inch needle), in packages of 10 TUBEX.

NDC 0008-0689-03, 10 mL vial, individually boxed.

NDC 0008-0689-04, 1 mL TUBEX (22 gauge x 1 1/4 inch needle), in packages of 10 TUBEX.

Protect from light

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

Directions for use of TUBEX® SYRINGE QUICK-LOADING 1 AND 2 ML SIZE To load the TUBEX Hypodermic Syringe



1. Grasp barrel of syringe in one hand. With the other hand, pull back firmly on plunger and swing the entire handle-section downward so that it locks at right angle to the barrel.



2. Insert TUBEX Sterile Cartridge-Needle Unit, needle end first, into the barrel. Engage needle ferrule by rotating it clockwise in the threads at front end of syringe.



3. Swing plunger back into place and attach end to the threaded shaft of the piston. Hold the syringe barrel with one hand and rotate plunger until both ends of TUBEX Sterile Cartridge-Needle Unit are fully, but lightly, engaged. To maintain sterility, leave the rubber sheath in place until just before use. To aspirate before injecting, pull back slightly on the plunger.

To Administer

Method of administration is the same as with conventional syringe. Remove rubber sheath, introduce needle into patient, aspirate and inject.

To remove the empty TUBEX



Replace sheath with a twisting motion to prevent needle from snagging. Disengage plunger from piston by rotating counter-clockwise, and open syringe as in step No. 1. Do not pull plunger back before disengaging or syringe will jam. Rotate TUBEX Cartridge-Needle Unit counterclockwise to disengage at front end of syringe, remove from syringe and discard.

To adapt 2 mL syringe to 1 mL TUBEX



The 2 mL syringe can be used for a 1 mL TUBEX. Engage both ends of TUBEX and push the slide through so the number "1" appears. After use, the syringe automatically resets itself for 2 mL TUBEX.

NOTE: Any graduated markings on TUBEX Sterile Cartridge-Needle Units are to be used as a guide in aspirating or administering measured doses.

Used TUBEX Cartridge-Needle Units should not be employed for successive injections or as multiple-dose containers. They are intended to be used only once and discarded. (Before discarding, the sheath-covered needle should be bent to seal the lumen in order to discourage pilferage or reuse.)

Wyeth does not recommend and will not accept responsibility for the use of any cartridge-needle unit other than TUBEX® in the TUBEX® Syringe.

Wyeth Laboratories Inc., Philadelphia, PA 19101



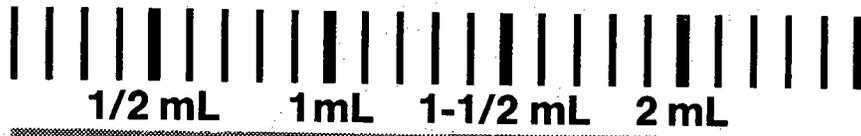
CI 3463-1

Issued July 18, 1985

Printed in USA

APPROVED

PH



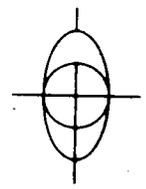
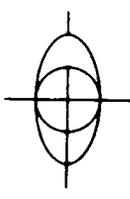
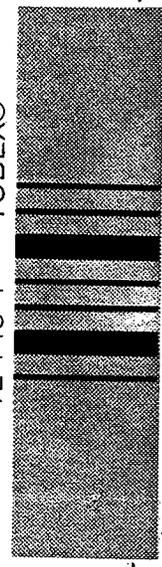
1/2 mL 1 mL 1-1/2 mL 2 mL

NALOXONE 0.04 MG
HCL INJECTION, USP PER TUBEX
(PEDIATRIC) (0.02 MG PER ML)

Wyeth®
PHILA.
FOR IV, IM,
OR SC USE

LOT EXP

TL 145-1 TUBEX®



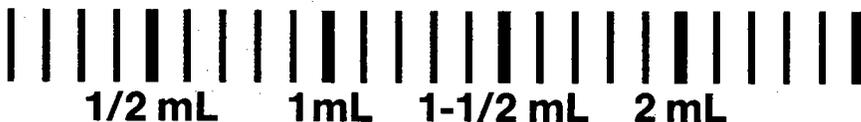
PHOTOCOMPOSING
JOB NO. 96423
FIRST PROOF
REDUCES ONE HALF

**BACKGROUND TINT FF-2
REVISED 12/84**

APPROVED

OCT 2 1985

BF
78

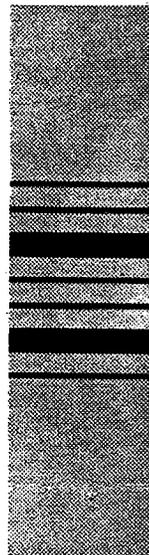


NALOXONE 0.04 MG
HCL INJECTION, USP PER TUBEX
(PEDIATRIC) (0.02 MG PER ML)

Wyeth®
PHILA.
FOR IV, IM,
OR SC USE

LOT EXP

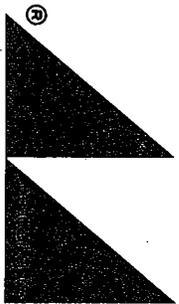
TL 145-1 TUBEX®



PHOTOCOMPOSING
JOB NO. 96423
FIRST PROOF
REDUCES ONE HALF

**BACKGROUND TINT FF-2
REVISED 12/84**

Wyeth
Naloxone
HCl Injection, USP
(Pediatric)



Wyeth®
Naloxone
HCl Injection, USP
(Pediatric)

TUBEX
NDC 0008-0688-02
25 gauge
5/8 inch needle

Wyeth
Naloxone
HCl Injection, USP
(Pediatric)
0.04 mg per TUBEX or 0.02 mg per mL

BEFORE INJECTING,
SEE PACKAGE INSERT
FOR ADMINISTRATION
INSTRUCTIONS.

for IV, IM, or SC use

Each mL contains, in sterile water for injection, 0.02 mg naloxone hydrochloride; 8.6 mg sodium chloride; and 2.0 mg methylparaben and propylparaben, as preservatives, in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

Usual Dosage: See enclosed information.
Caution: Federal law prohibits dispensing without prescription.

Do not use if solution is discolored or contains a precipitate

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

Protect from light

Use this carton to protect contents from light.

Each TUBEX® Sterile Cartridge-Needle Unit includes one sterile TUBEX hypodermic needle (25 gauge, 5/8 inch)

WYETH LABORATORIES INC.
Philadelphia, PA 19101

0.04 mg
per TUBEX or
0.02 mg per mL

Ten—2 mL size
25 gauge
5/8 inch needle

0.04 mg per TUBEX® or
0.02 mg per mL

BEFORE INJECTING,
SEE PACKAGE INSERT
FOR ADMINISTRATION
INSTRUCTIONS.

NDC 0008-0688-02

Wyeth
Naloxone
HCl Injection, USP
(Pediatric)

0.04 mg
per TUBEX or
0.02 mg per mL

TUBEX
NDC 0008-0688-02
25 gauge
5/8 inch needle

Made and printed
in USA
UK 9528-1

Wyeth
Naloxone
HCl Injection, USP
(Pediatric)

LOT

0.04 mg per TUBEX
or 0.02 mg per mL
25 gauge
5/8 inch needle

EXP



APPROVED
OCT 2 1985

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

70-189

CSO LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING
ANDA-DRAFT

DATE OF REVIEW: March 27, 1985

ANDA#: 70-189

NAME OF FIRM: Wyeth

NAME OF DRUG: Generic: Naloxone Hydrochloride Injection, USP

DATE OF SUBMISSION: January 3, 1985

COMMENTS:

Carton: Not Satisfactory

1. Add, "For I.V., I.M. or S.C. Use", directly under "0.02 mg per ml"
2. "0.04 mg _____ rather than "0.02 mg per ml").

Container: Not Satisfactory

1. Add "For I.V., I.M. or S.C. Use", directly under "0.04 mg per Tubex or 0.02 mg per ml"

Insert: Not Satisfactory

1. HOW SUPPLIED

1. Add "Protect From Light" and "Store at Controlled Room Temperature, 15^o-30^oC (59^o-86^oF)"
[21 CFR 201.57(k)(4)]

RECOMMENDATIONS:

1. Inform firm of these comments.
2. Request that they revise their carton and container labels and package insert labeling, then prepare and submit FPL.

R. Brown

cc: DUP
RBROWN/jt/4-8-85
1000A

REVIEW OF PROFESSIONAL LABELING

Original Amendment - FPL

DATE OF REVIEW: August 16, 1985

ANDA/NDA #: 70-188 (0.02 mg/mL vial) NAME OF FIRM: Wyeth
70-189 (0.02 mg/mL Tubex^R)
70-190 (0.4 mg/mL vials)
70-191 (0.4 mg/mL, Tubex^R)

NAME OF DRUG: Generic: Naloxone Hydrochloride Injection, USP

DATE OF SUBMISSION: August 16, 1985

COMMENTS:

Carton: Satisfactory

Container: Satisfactory

Insert: We advise you to review the exclusivity information on this product as noted in the 10th supplement of Approved Prescription Drug Products. This recent new information may influence your labeling and/or effective date of any future approval. The exclusivity issue is currently under review by the Agency.

RECOMMENDATIONS:

1. Inform firm of the above comments.
2. Approval of this application cannot be given until the exclusivity issues in regard to labeling have been resolved.

Ron Brown
Ron E. Brown

RBrown/sr/8/20/85
0920A

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

70-189

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW <small>(If necessary, continue any item on 8" x 10 1/2" paper. Key continuation to item by number.)</small>		1. ORGANIZATION	2. NDA NUMBER
		GENERIC DRUG	70-189
3. NAME AND ADDRESS OF APPLICANT (City and State)		4. AF NUMBER	
WYETH LABORATORIES, INC. P.O. BOX 8299 PHILADELPHIA, PENN. 19101			
6. NAME OF DRUG		5. SUPPLEMENT (S)	
NALOXONE - HCl		NUMBER(S)	DATE(S)
8. SUPPLEMENT(S) PROVIDES FOR:		9. AMENDMENTS AND OTHER (Reports, etc.) DATES	
NA			
10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF(S)	
NARCOTIC ANTAGONIST	<input checked="" type="checkbox"/> RX <input type="checkbox"/> OTC	70-188	
13. DOSAGE FORM (S)	14. POTENCY (see)	190	
INJECTION	0.02mg/ml, 2ml tubes.	191	
15. CHEMICAL NAME AND STRUCTURE		16. RECORDS AND REPORTS	
		CURRENT	
		<input type="checkbox"/> YES <input type="checkbox"/> NO	
		REVIEWED	
		<input type="checkbox"/> YES <input type="checkbox"/> NO	
17. COMMENTS			
APPEARS THIS WAY ON ORIGINAL			
18. CONCLUSIONS AND RECOMMENDATIONS			
Not approvable			
19. NAME		REVIEWER SIGNATURE	DATE COMPLETED
BART HO		Bart Ho	4/12/85
DISTRIBUTION <input type="checkbox"/> ORIGINAL JACKET <input type="checkbox"/> REVIEWER <input type="checkbox"/> DIVISION FILE			

CHEMIST'S REVIEW, Page 2

Enter evaluation or comments for each item. If necessary, continue on 8" x 10 1/2" paper. Key continuation to item by number. Enter "NC" if no change or "NA" if not applicable.

NDA NUMBER
70-789

20. COMPONENTS AND COMPOSITION (6, 7)

SEE Attached.

21. FACILITIES AND PERSONNEL (8a,b)

Refer to DMF — ~~no~~ brief description provided in a amendment, satisfactory

22. SYNTHESIS (8c)

Manufacturer = _____, DMF —, reviewed, needs up

Active ingredient = certificate of analysis ~~is~~ provided, satisfactory

23. RAW MATERIAL CONTROLS (8d,e)

a. NEW DRUG SUBSTANCE

active ingredient = according to USP ~~and~~ and conforms to USP ~~no~~ specs, no result

b. OTHER INGREDIENTS

NF = Hcl, parabens,

USP = Nacl, H2O

> said to test ^{and conform} according to USP/NF monographs no specs, no test results shown. of what test they run.

24. OTHER FIRM(S) (8f)

25. MANUFACTURING AND PROCESSING (8g,h,i,k)

Manufacturing procedure attached, satisfactory (Page 38)

26. CONTAINER (8j)

Glass vial = USP _____

Rubber components = _____

(and suitable test.)

DMF given. NO FDEC station

27. PACKAGING AND LABELING (8l,m)

28. LABORATORY CONTROLS (In-Process and Finished Dosage Form) (8n)

active ingredient = USP & Firm alternate type method.

parabens, hydroxymorphone Hcl = _____ others = USP or NF

No actual specs or tests submitted

29. STABILITY (8p)

Data submitted most up to 18 month, some 3 month, 6 month

Request for 24 month expiration date.

30. CONTROL NUMBERS (8q)

No batch No. submitted.

31. SAMPLES AND RESULTS (8r)

a. VALIDATION — method needs validated

b. MARKET PACKAGE

32. LABELING (8s)

Reviewed by R. Brown, not satisfactory

33. ESTABLISHMENT INSPECTION

1. Wpeth Labs. Inc. on the alert list of March 25, 1985 inspected, satisfactory.

34. RECALLS

November 29, 1984

024

ARTICLES USED AS COMPONENTS OF

Naloxone Hydrochloride Injection, USP

0.02 mg Naloxone Hydrochloride per mL

(Form FD-356, paragraph 6)

*Naloxone Hydrochloride, USP,
Sodium Chloride, USP
Methylparaben, NF
Propylparaben, NF
Hydrochloric Acid, NF
Water for Injection, USP

[]

Note: Refer to Drug Master File No. _____ for

[]

APPEARS THIS WAY
ON ORIGINAL

11/29/84 - COMPOSITION OF DRUG

November 29, 1984
026

COMPOSITION OF

Naloxone Hydrochloride Injection, USP

0.02 mg Naloxone Hydrochloride per mL

(Form FD-356, paragraph 7)

<u>Per mL</u>		<u>Per _____ (4)</u>
0.02 mg	Naloxone Hydrochloride, USP, (1) (2) (3)	_____
8.6 mg	Sodium Chloride, USP	_____
_____	Methylparaben, NF	_____
_____	Propylparaben, NF	_____
q.s. to pH _____	Hydrochloric Acid, NF	q.s. to pH _____
	— solution prepared using Water	
	for Injection, USP)	
q.s. ad 1.0 mL	Water for Injection, USP	q.s. ad _____

- (1) _____
- (2) _____ mg of Naloxone Hydrochloride USP, _____ may be used.
- (3) The amount of Naloxone Hydrochloride, USP used per batch is corrected to 100% based on purity when below 100%.
- (4) This is the maximum batch size; smaller batches will be prepared using proportional quantities.

APPEARS THIS WAY
ON ORIGINAL

CHEMIST'S REVIEW NDA 70-189

3. NAME AND ADDRESS OF APPLICANT

Wyeth Laboratories, Inc.
P.O. Box 8299
Philadelphia, Penn. 19101

6. NAME OF DRUG

Naloxone HCT

8. SUPPLEMENT(S) PROVIDE(S) FOR:

N/A

10. PHARMACOLOGICAL CATEGORY

Narcotic Antagonist

11. HOW DISPENSED

Rx

12. RELATED IND/NDA/DMF(S)

70-188

70-190

70-191

13. DOSAGE FORM(S)

Injection

14. POTENCY

0.2 mg/ml, 2 ml Tubex

18. CONCLUSIONS AND RECOMMENDATIONS

Not Approvable

19. REVIEWER:

Bart Ho
4-12-85

DATE COMPLETED:

APPEARS THIS WAY
ON ORIGINAL

Redacted 2

4/12/85
chem
RW

Page(s) of trade

secret and /or

confidential

commercial

information

CHEMIST REVIEW 70-189

NAME AND ADDRESS OF APPLICANT

Wyeth Laboratories
P.O. Box 8299
Philadelphia, Penn 19101

PURPOSE OF AMENDMENT

1. Labeling
2. Answering to my questions in letter of April 26, 1985

NAME OF DRUG

Naloxone HCl

HOW DISPENSED

Rx

DOSAGE FORM

Injection

POTENCY

0.02 mg/ml

RELATED IND/DMF/NDA

70-188, 189, 190, 191

LABELING

Not Satisfactory R Brown June 27, 1985

ESTABLISHMENT INSPECTION

Called to Inspection Branch to verify the status of manufacturing facility at _____

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

Specs of Finished dosage form submitted, Satisfactory

PACKAGING

Tests on rubber components submitted, FD&C statement submitted, Satisfactory

REMARKS AND CONCLUSIONS

Not Approvable

REVIEWER

Bart Ho, Ph.D.

B. Ho

DATE

7/11/85

APPEARS THIS WAY
ON ORIGINAL

CHEMIST REVIEW 70-189

NAME AND ADDRESS OF APPLICANT

Wyeth Laboratories
P.O. box 8299
Philedelphia, PA 19101

HOW DISPENSED

Rx

PHARMACOLOGICAL CATEGORY

Narcotic Antagonist

NAME OF DRUG

NaIoxone HCL

RELATED IND/NDA/DMF

70-188, 189, 190, 191

DOSAGE FORM

Injection

POTENCY

0.02 mg/ml 2ml Tubex

SAMPLES

Found acceptable by NY District for drug substance from
Results included, September 11, 1985

LABELING

Satisfactory, R. Brown August 16, 1985
Results included, September 11, 1985.

BIOLOGIC AVAILABILITY

Waiver

ESTABLISHMENT INSPECTION

Approved January 16, 1985
Also, confirmed by Tel. Conversation with _____ on
September 13, 1985. Manufacture Review Branch. Inspection results
included.

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROL

PACKAGING

Satisfactory, R. Brown, August 16, 1985.

CHEMIST REVIEW PAGE 2

STABILITY

Protocol: Satisfactory
Exp. Date: 18 months

REMARKS AND CONCLUSIONS

Both chemistry and labeling review satisfactory
Bio waiver

Approve conditionally, pending on the review of exclusivity issue

REVIEWER

Bart Ho, Ph.D.

DATE

APPEARS THIS WAY
ON ORIGINAL

November 29, 1984

027

COMPOSITION OF

Naloxone Hydrochloride Injection, USP

0.02 mg Naloxone Hydrochloride per mL

(Form FD-356, paragraph 7)

<u>Per mL</u>		<u>Per _____</u> (4)
0.02 mg	Naloxone Hydrochloride, USP, (1) (2) (3)	_____
8.6 mg	Sodium Chloride, USP	_____
_____	Methylparaben, NF	_____
_____	Propylparaben, NF	_____
q.s. to pH _____	Hydrochloric Acid, NF	q.s. to pH _____
	—solution prepared using Water	
q.s. ad 1.0 mL	for Injection, USP)	
	Water for Injection, USP	q.s. ad _____

(2) _____ of Naloxone Hydrochloride USP, _____ may be used.

(3) The amount of Naloxone Hydrochloride, USP used per batch is corrected to 100% based on purity when below 100%.

(4) This is the maximum batch size; smaller batches will be prepared using proportional quantities.

November 29, 1984

025

ARTICLES USED AS COMPONENTS OF

Naloxone Hydrochloride Injection, USP

0.02 mg Naloxone Hydrochloride per mL

(Form FD-356, paragraph 6)

*Naloxone Hydrochloride, USP,
Sodium Chloride, USP
Methylparaben, NF
Propylparaben, NF
Hydrochloric Acid, NF
Water for Injection, USP

Note: Refer to Drug Master File No. _____ for

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

70-189

**BIOEQUIVALENCE
REVIEW(S)**

2 / 19 / 85

Naloxone Hydrochloride Injection
U.S.P. (Pediatric)
ANDA # 70-188
0.02 mg/ml in 2 ml vials
ANDA # 70-189
0.02 mg/ml in 2 ml tubex
ANDA #70-190
0.4 mg/ml in 1 ml and 10 ml vials
ANDA #70-191
0.4 mg/ml in 1 ml tubex
Reviewer: Sikta Pradhan, Ph.D.
Wang #4702e

Wyeth Laboratories, Inc.
Philadelphia, PA 19101
Submission Date:
January 3, 1985

REVIEW OF A REQUEST FOR WAIVER

The firm has requested a waiver of the in-vivo bioavailability study requirements for its Naloxone Hydrochloride Injection, USP (Pediatric), 0.02 mg/ml in 2 ml vials 0.02 mg/ml in 2 ml tubex, 0.4 mg/ml in 1 ml and 10 ml vials and 0.4 mg/ml in 1 ml tubex under CFR 320.22.

Comments:

1. The formulation of the test product and the innovator product, Narcan^R Neonatal injection, 0.02 mg/ml - NAA #16-636 are presented in Table I. The formulation, dosage form, route of administration of this product are essentially identical to NARCAN^R (Du Pont Pharmaceuticals product).
2. The test product should be labeled for intravenous, subcutaneous or intramuscular administration.

Recommendation:

The Division of Bioequivalence finds that the information submitted by Wyeth Laboratories, Inc. demonstrates that its Naloxone Hydrochloride, 0.02 mg/ml in 2 ml vial injection falls under Section 320.22 (b) of the bioavailability/bioequivalence regulations published in the CFR. The Division of Bioequivalence recommends that waiver of in-vivo bioavailability be granted. Accordingly, a bioavailability study need not be undertaken.

Sikta Pradhan

Sikta Pradhan
Division of Bioequivalence

RD INITIALED BY CISE
FT INITIALED BY CISE

C. M. Je

SPradhan/cc/Wang #4702e/1-31-85

cc: ANDA 70-188, 70-189, 70-190, 70-191 orig., HFN-230 (4), HFN-227 (Pradhan, Ise-2), HFN-200 (Hare), HFN-223 (Shah-FOI), drug file

APPEARS THIS WAY
ON ORIGINAL

Table I

Comparative Formulation

Test Product Formulation

Ingredient

(a) Drug Concentration, 0.02 mg/ml

Naloxone Hydrochloride Injection U.S.P. (Pediatric)	0.02 mg/ml
Sodium Chloride, U.S.P.	8.6 mg/ml
Methylparaben, NF	<u> </u>
Propylparaben, NF	<u> </u>

HCl, NF q.s. to pH — HCl solution prepared using water, USP)

Water for Injection, USP q.s. ad 1.0 ml

Each vial or tubex contains 2 ml of Naloxone Hydrochloride solution for injection.

(b) Drug Concentration, 0.4 mg/ml

Naloxone Hydrochloride Injection U.S.P.	0.4 mg/ml
Sodium Chloride, U.S.P.	8.6 mg/ml
Methylparaben, NF	<u> </u>
Propylparaben, NF	<u> </u>

HCl, NF q.s. to pH — HCl solution prepared using water, U.S.P.)

Water for Injection, U.S.P. q.s. ad 1.0 ml

Each vial contains 1 ml or 10 ml, and each tubex contains 1 ml of Naloxone Hydrochloride solution for injection.

APPEARS THIS WAY
ON ORIGINAL

Innovator Product Formulation

Ingredient

Narcan^R (Du Pont Pharmaceuticals)

Available as a sterile solution for intravenous, intramuscular and subcutaneous administration in two concentrations.

(a) Drug Concentration, 0.02 mg/ml

Naloxone - HCl	0.02 mg/ml
Sodium Chloride	8.6 mg/ml
Methylparaben	<u> </u>
Propylparaben	<u> </u>

pH adjusted to with hydrochloric acid.

(b) Drug Concentration, 0.4 mg/ml

Naloxone - HCl	0.4 mg/ml
Sodium Chloride	8.6 mg/ml
Methylparaben	<u> </u>
Propylparaben	<u> </u>

pH adjusted to with hydrochloric acid

**APPEARS THIS WAY
ON ORIGINAL**

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

70-189

**ADMINISTRATIVE
DOCUMENTS**



Memorandum

TO :Manufacturing Review Branch (HFN-322) DATE: 1/16/85
Division of Drug Quality Compliance
FROM :Division of Generic Drugs
Requester's Name David L. Rosen (DFW) PHONE: 443-4080
SUBJECT: ESTABLISHMENT EVALUATION REQUEST

NDA, ANDA, AND SUPPLEMENT NUMBER: 70-188; 70-189; 70-190; 70-191

DRUG TRADE MARK (if any)

DRUG NONPROPRIETARY NAME: Naloxone Hydrochloride Injection USP, 0.02 mg/ml & 0.4 mg/ml

DOSAGE FORM AND STRENGTH(S): SVP

DRUG CLASSIFICATION: (Priority) A or B 1C Other PROFILE CLASS CODE:

APPLICANT'S NAME: Wyeth Laboratories
ADDRESS: Wasp & Biddle Streets, Marietta, PA

FACILITIES TO BE EVALUATED: (Name, Full Address, DMF# (if any), and Responsibility)

- 1. applicant - mfr finished dosage form, dmf
2. dmf

Comments: () See Attached.
() Actual on-site inspection requested.

Reason:

FOR HFN-322 USE ONLY:

Request Rec'd: Inspection Requested:
(if applicable)

Firm(s) are in Compliance With GMPs:

Basis for Decision:

Reviewing CSO: Concurrence:

cc: HFN-
HFN-
HFN-322

HFC-131 D. Jarrow

Redacted

2

9/13/85
manufacturing
process

Page(s) of trade

secret and /or

confidential

commercial

information

After discussing and evaluating each option, it was decided that the Agency would allow the exclusivity request to stand, proceed with the approval process and make any final approvals effective 9/24/86.

This decision will be incorporated in any future letters to all pending applications for Naloxone Hydrochloride Injection.


Thomas B. Poux

Concur: 

Attendees:

T. Scarlett, Esq.
D. Beers, Esq.
G. Knapp - HFN-205
D. Hare - HFN-203
J. Morrison - HFN-201
E. Dutra, Esq. - HFN-364
M. Watson - HFN-360

cc:

M. Seife - HFN-230
K. Johnson - HFN-231
D. Rosen - HFN-232
J. Meyer - HFN-233

TPoux/mk/9/10/85/0552m

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE

9/27/85

NDA NUMBER 70-185 70-190
 70-189 70-191
 IND NUMBER

The Division of Biologics granted a waiver of in vivo bioequivalency study requirements in its 2/19/85 decision and the firm was informed of this in our 2/25/85 letter. This record confirms the fact that the proposed products in the aforementioned ANDAs are deemed bioequivalent to the innovator product. R Pollock 9/27/85

TELECON/MEETING

INITIATED BY

- APPLICANT/SPONSOR
- FDA

METHOD

- BY TELEPHONE
- IN PERSON

PRODUCT NAME

NALOXONE HCL INT. USP
 0.02mg/ml in 2ml vials and 10ml
 0.4mg/ml in 1ml & 10ml vials
 and tubing

FIRM NAME

Wyeth Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

TELEPHONE NO.

APPEARS THIS WAY ON ORIGINAL

SIGNATURE

Robert Pollock

HFN-230
 443-4080

DIVISION

DGD

**NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT**

NDA NUMBER

70-189

DATE APPROVAL LETTER ISSUED

OCT 2 1985

TO:

Press Relations Staff (HF1-40)

FROM:

Bureau of Drugs

Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION

ORIGINAL NDA SUPPLEMENT TO NDA ABBREVIATED ORIGINAL NDA SUPPLEMENT TO ANDA

CATEGORY

HUMAN VETERINA

TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG.

Naloxone Hydrochloride

DOSAGE FORM

Injections

HOW DISPENSED

RX OTC

ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)

Naloxone Hydrochloride, 0.02 mg/ml in 2 ml Tubex.

NAME OF APPLICANT (Include City and State)

Wyeth Laboratories
Philadelphia, Pennsylvania 19101

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Narcotic Antagonist

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME

Bart Ho, Ph.D

DATE

FORM APPROVED BY

NAME

Jack Meyer

DATE

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

70-189

CORRESPONDENCE

WYETH LABORATORIES INC.



P.O. Box 8299, Philadelphia, Pennsylvania 19101
(215) 688-4400

REGULATORY AFFAIRS

December 28, 1984

ORIGINAL

Marvin Seife, M. D., Director
Division of Generic Drugs
Office of Drug Standards
Food and Drug Administration
Center for Drugs and Biologics
HFN 230, Room 16-70
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Seife:

We are submitting herewith an Abbreviated New Drug Application for Naloxone Hydrochloride Injection, USP (Pediatric), 0.02 mg/ml in 2 ml Tubex®. Our new generic version is identical to the pioneer drug (DuPont's Narcan® Neonatal Injection, 0.02 mg/ml - NDA No. 16-636) with respect to active and inactive ingredient formulation, route of administration, dosage form, dosage strength, and condition of use recommended in the labeling. A separate application covering the same product and strength packaged in 2 ml vials is being submitted concurrently under separate cover. *Labeling statement in labeling section 1602b*

In accordance with the requirement of Section 505(j)(2)(A)(vii) of the Federal Food, Drug, and Cosmetic Act, the applicant hereby certifies in its opinion and to the best of its knowledge that no patent information has been filed pursuant to Section 505(b) or (c) concerning naloxone hydrochloride injection or its use. Should the listing when published include patent information, this application will be amended.

As provided for in 21 CFR Part 320.22 (C) (2), we request a waiver of the in vivo bioavailability requirements for Naloxone Hydrochloride Injection 0.02 mg/ml. This waiver is requested on the basis that the drug product covered by this ANDA is identical in both active and inactive ingredient formulation to that drug as currently approved in a full new drug application (DuPont's Narcan® Neonatal Injection, 0.02 mg/ml - NDA No. 16-636).

In support of this ANDA we will test the stability of production batches of the product at reasonable intervals, submit the results of these studies with our periodic reports for the Application, and promptly withdraw from the market any lots that are found to be subpotent.

We trust that you will find this application satisfactory and that it may be approved at your earliest convenience.

Sincerely,

WYETH LABORATORIES INC:

Joseph N. Bathish
Joseph N. Bathish
Director, Regulatory Affairs

RECEIVED

JAN 3 1985

GENERIC DRUGS

JNB/ad
2092A

Chris

WYETH LABORATORIES INC.



P.O. Box 8299, Philadelphia, Pennsylvania 19101
(215) 341-4291
(215) 341-4292

REGULATORY AFFAIRS

CONTROLLED

September 17, 1985

NDA No. 70-189

Marvin Seife, M.D., Director
Division of Generic Drugs
Office of Drug Standards
Food and Drug Administration
Center for Drugs and Biologics
HFN 230, Room 16-70
5600 Fishers Lane
Rockville, MD 20857

NDA ORG AMENDMENT

Dear Dr. Seife:

Reference is made to our pending Abbreviated New Drug Application for Naloxone Hydrochloride Injection, USP 0.02 mg/ml in 2 ml Tubex® (NDA No. 70-189) and to a September 6, 1985 informal meeting between Mr. Meyer and Dr. Ho of your Division and Ms. Lepri of Wyeth.

During this meeting, two comments were presented relative to our proposed — assay for Naloxone Hydrochloride Injection. They concerned the solubility of the reference standard in the Standard Preparation and the concentrations of the components in the System Suitability Test (see attached). In a telephone conversation of September 13, 1985 between Dr. DeAngelis (Wyeth), Ms. Lepri and Dr. Ho, the reviewer's comments were discussed and the following agreements were reached:

- (1) The Standard Preparation will be modified to assure solubility of the reference standard. To accomplish this, the method will direct that the reference standard be ~~_____~~ rather than ~~_____~~. This is actually how Wyeth performs the assay, but an error was made in the method write-up.

(2)

[]

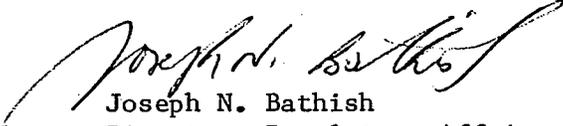
main on scale and the necessary calculations can be conveniently made.

Attached are revisions in the naloxone hydrochloride assay methods that incorporate the above discussed modifications.

We trust that you will find this information satisfactory.

Sincerely,

WYETH LABORATORIES INC.



Joseph N. Bathish
Director, Regulatory Affairs

JNB:dlj
Attachment

RECEIVED

SEP 19 1985

GENERIC DRUGS

Or

WYETH LABORATORIES INC.



P.O. Box 8299, Philadelphia, Pennsylvania 19101
(215) 341-4291
(215) 341-4292

REGULATORY AFFAIRS

August 12, 1985

NDA No. 70-189

Marvin Seife, M. D., Director
Division of Generic Drugs
Office of Drug Standards
Food and Drug Administration
Center for Drugs and Biologics
HFN 230, Room 16-70
5600 Fishers Lane
Rockville, MD 20857

RESUBMISSION
NDA ORIG AMENDMENT

EPL

Dear Dr. Seife:

Reference is made to our pending Abbreviated New Drug Application for Naloxone Hydrochloride Injection, USP 0.02 mg/ml in 2 ml Tubex[®] (NDA No. 70-189) and to your letter of July 15, 1985 in which labeling deficiencies were listed.

We are pleased to provide herewith twelve specimens of each of the following final printed labeling components, revised in accordance with the labeling comments addressed in your letter of July 15, 1985.

1. Package Insert
2. Tubex[®] Label (proof copies in lieu of printed on glass specimens)
3. Carton

Other than the changes requested in your July 15, 1985 letter, the labeling format and content employed in each of the above components is consistent with the draft copies we previously submitted to your Administration.

We trust that this provides the balance of the information that is needed for final approval of this ANDA.

Sincerely,

WYETH LABORATORIES INC.

Joseph N. Bathish
Director, Drug Regulatory Affairs

RECEIVED

AUG 13 1985

GENERIC DRUGS

JNB:dlj

NDA 70-189

JUL 15 1985

Wyeth Laboratories, Inc.
Attention: Joseph N. Bathish
P.O. Box 8299
Philadelphia, Pennsylvania 19101

Dear Mr. Bathish:

Please refer to your abbreviated new drug application dated June 24, 1985, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for the preparation Maloxone Hydrochloride Injection, 0.02 mg/ml in 2 ml Tubex.

The application is deficient and therefore not approvable under Section 505(j)(3) of the Act as follows:

Labeling has been reviewed, in this regard:

- Carton: Not Satisfactory
1) Delete the phrase, "_____ which precedes "2.0 mg methylparaben and propylparaben, . . ."
- Container: Satisfactory
- Insert: Not Satisfactory
1) DESCRIPTION
a. Revise the chemical name in accord with the 2nd name listed for Maloxone HCl in USP XXI.
b. Same as item 1 under carton.
2) HOW SUPPLIED:
a) A description of the needle supplied with the Tubex[®] cartridge should be given.
b) For 10 mL Vial: Revise to read, . . . individually boxed (rather than,

RECOMMENDATIONS:

Revise your carton and package insert labeling, then prepare and submit final printed labeling.

The file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized, which represents the information necessary to remove all deficiencies we have outlined.

If you do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.120(d). If you do so, the application shall be re-evaluated and within 90 days of the date of receipt of such request (or additional period as we may agree upon), the application shall be approved or you shall be given a written notice of opportunity for a hearing on the question of whether the application is approvable.

Sincerely yours,

Harvin Seife /for

7-15-85

Harvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

PHI-DO

HFN-83

HFN-230

Q&B
7/10/85

B.H.O.
R/Brown/JMeyer/BHo

R/D INITIALED BY: JMeyer/MSeife

D Utz: 7-9-85 (0520R)

NOT APPROVED

JMeyer 7/12/85

WYETH LABORATORIES INC.

REGULATORY AFFAIRS



P.O. Box 8299, Philadelphia, Pennsylvania 19101
(215) 341-4291
(215) 341-4292

ONS

June 24, 1985

NDA 70-189

Marvin Seife, M.D., Director
Division of Generic Drugs
Office of Drug Standards
Food and Drug Administration
Center for Drugs and Biologics
HFN 230, Room 16-70
5600 Fishers Lane
Rockville, MD 20857

RESUBMISSION
NDA ORIG AMENDMENT
DRAFT LABELING

Dear Dr. Seife:

Reference is made to our pending Abbreviated New Drug Application for Naloxone Hydrochloride Injection, USP 0.02 mg/ml in 2 mL Tubex® (NDA No. 70-189) and to your letter of April 26, 1985 in which the manufacturing, controls, and labeling deficiencies were listed.

As requested in this correspondence, we are pleased to provide herewith, in triplicate, the following information:

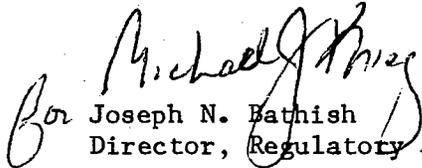
1. Revised draft carton and container labeling.
2. Revised direction circular.
3. With regard to the _____, USP XXI Physicochemical Test results.
4. A statement from the _____ indicating that the rubber compositions are in conformity with current Food Additive Regulations.
5. Explanation of the relationship between experiment numbers and bulk batch numbers.
6. Actual test and specifications performed according to USP XXI on the finished dosage form.
7. Designation of the testing method used for assay of the stability samples.
8. A current GMP status statement.
9. In response to Item 2(e), page 104 corrects a typographical error.

Also, in a meeting held on May 8, 1985 between Mr. Meyer and Dr. Ho of your Division and Ms. Lepri of Wyeth it was agreed that various items in the aforementioned letter have been adequately answered by previous submissions, and Wyeth would respond to those items by referencing the appropriate amendment and/or original ANDA. In this regard, we wish to advise that for Items 2(a) and 3(b) please refer to our April 1, 1985 and April 26, 1985 amendments. Concerning Items 2(b) and (c), reference is made to our original submission dated December 28, 1984, pages 34-45 and page 33, respectively.

We trust that this provides the balance of the information requested from Wyeth relative to this pending ANDA and that the application may now be considered approvable.

Sincerely,

WYETH LABORATORIES INC.

For 
Joseph N. Bathish
Director, Regulatory Affairs

JNB:tja
Enclosures

RECEIVED

JUN 25 1985

GENERIC DRUGS

NDA 70-189

Wyeth Laboratories, Inc.
Attention: Joseph H. Bathish
P.O. Box 8299
Philadelphia, Pennsylvania 19101

MAY 14 1985

Gentlemen:

Reference is made to your communication dated April 26, 1985, regarding your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Naloxone Hydrochloride Injection, 0.02 mg/ml in 2 ml Tubex.

The communication enclosed the following:

1. Safety and toxicity data with respect to _____
2. A letter from _____ that _____ conforms to USP XXI.

The material submitted is being retained as part of your application.

Sincerely yours,

Marvin Seife 5/14/85
Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

PHI-DO

HFN-83

HFN-230

JMeyer/BHo

R/D INITIALED BY: JMeyer/MSeife

D Utz: 5-13-85 (0116R)

ACK/RET

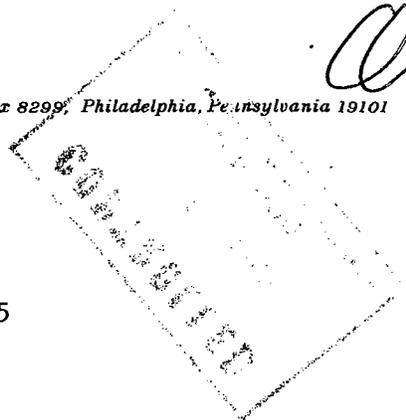
B.Ho JMeyer 5/13/85

WYETH LABORATORIES INC.



P. O. Box 8299, Philadelphia, Pennsylvania 19101

Orig



April 26, 1985

NDA NO. 70-189

Marvin Seife, M.D., Director
Division of Generic Drugs
Office of Drug Standards
Food and Drug Administration
Center for Drugs and Biologics
HFN 230, Room 16-70
5600 Fishers Lane
Rockville, MD 20857

NDA ORIG AMENDMENT

Dear Dr. Seife:

Reference is made to our pending Abbreviated New Drug Application for Naloxone Hydrochloride Injection, USP (Pediatric), 0.02 mg/ml in 2 ml Tubex[®] (NDA No. 70-189).

We wish to amend this application to provide herewith, in triplicate, the following information:

1. With respect to the _____ a description of the safety evaluation conducted by the _____ data for each _____
2. A letter from _____ indicating that the _____ conforms to USP XXI standards.

We trust that you will find this information satisfactory and that the application may now be considered approvable.

Sincerely,

WYETH LABORATORIES INC.

For *Michael J. Kueg*
Joseph N. Bathish
Director, Regulatory Affairs

JNB:tja
Enclosures

RECEIVED

APR 29 1985

GENERIC DRUGS

APR 26 1985

Wyeth Laboratories, Inc.
 Attention: Joseph M. Bathish
 P.O. Box 8299
 Philadelphia, Pennsylvania 19101

Gentlemen:

Please refer to your abbreviated new drug application dated December 28, 1984, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for the preparation Maloxone Hydrochloride Injection, 0.02 mg/ml in 2 ml Tubex.

Reference is made to your communication dated April 1, 1985.

The application is deficient and therefore not approvable under Section 505(j)(3) of the Act as follows:

1. Labeling has been reviewed. In this regard:

Carton: Not Satisfactory

1. Add, "For I.V., I.M. or S.C. Use", directly under "0.02 per mL."
2. "0.04 mg _____" rather than "0.02 mg per mL."

Container: Not Satisfactory

1. Add "For I.V., I.M. or S.C. Use", directly under "0.04 mg per Tubex or 0.02 mg per mL."

Insert: Not Satisfactory

1. Add "Protect From Light" and "Store at Controlled Room Temperature, 15°-30°C (59°-86°F)" [21 CFR 201.57 (k)(4)].

2. Assurance that the drug dosage form and components will comply with the specifications and tests described in an official compendium, if such article is recognized therein, or if not listed, or if the article differs from the compendium drug, that the specifications and tests applied to the drug and its components are adequate to assure their identity, strength, quality and purity. In this regard:

- a. DNF / _____ fails to include a tests and specifications sheet according to USP XXI.
- b. It fails to submit an actual batch production sheet as part of this application.

-Page 2-

- c. It fails to submit the actual tests and specifications performed according to USP XXI on the active ingredient and other _____.
 - d. It fails to submit the actual test and specifications performed according to USP XXI on finished dosage form.
 - e. On page 104, it stated "Verapamil Hydrochloride Injecton, USP". Please clarify.
3. It fails to include a description of containers and materials used for packaging and adequate information with respect to the characteristics of, and test methods employed for, the container, closure, or other component parts of the drug package to assure their suitability for the intended use. In this regard: _____
_____ fail to provide:
- a. An updated tests and specifications of the _____ they supplied.
 - b. Biological evaluations of the stoppers and container.
 - c. A statement that components are in conformity with current Food Additive Regulations.
4. We note the alternate assay procedure for the finished dosage form. In this regard, it must be understood that the official compendium procedure will be employed by compliance for regulatory purpose.
5. In your stability studies:
- a. Explain the Exp. No. in relating to the batch No.
 - b. Specify the testing method used.
6. Clarify your current GMP status.

The file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized, which represents the information necessary to remove all deficiencies we have outlined.

APPEARS THIS WAY
ON ORIGINAL

If you do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.110(d). If you do so the application shall be re-evaluated and within 90 days of the date of receipt of such request (or additional period as we may agree upon), the application shall be approved or you shall be given a written notice of opportunity for a hearing on the question of whether the application is approvable.

Sincerely yours,

Harvin Seife 4/26/85
Harvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

PHI-DO
HFN-83
HFN-230
JMeyer/BHo
R/D INITIALED BY: JMeyer/MSeife
D Utz: 4-16-85 (0855B)
NOT APPROVABLE

Labeling
R.S. Barber
4/24/85

JMeyer 4/28/85
B. Ho

WYETH LABORATORIES INC.

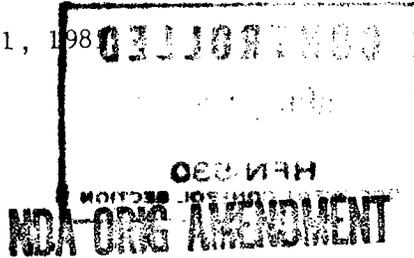


P.O. Box 8299, Philadelphia, Pennsylvania 19101
(215) 341-2191
(215) 341-2192

REGULATORY AFFAIRS

Aug

April 1, 1980



NDA No. 70-189

Marvin Seife, M.D., Director
Division of Generic Drugs
Office of Drug Standards
Food and Drug Administration
Center for Drugs and Biologics
HFN 230, Room 16-70
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Seife:

Reference is made to our pending Abbreviated New Drug Application for Naloxone Hydrochloride Injection, USP (Pediatric), 0.02 mg/ml in 2 ml Tubex[®] (NDA No. 70-189).

We wish to amend this application to provide herewith, in triplicate, the following information:

1. A brief description of Wyeth Laboratories manufacturing facility located in Marietta, PA.
2. A statement indicating that our Naloxone Hydrochloride Injection, USP conforms to USP XXI.
3. Segregated stability section containing only data relative to the above strength and closure system.
4. With respect to the _____ a description of the safety evaluation conducted by _____
5. Date of manufacture for each of the drug products covered in the stability data section.
6. Revised packaging section containing only packaging component information for the above specific container/closure system.
7. A statement from _____ indicating that the _____



Marvin Seife, M.D., Director
NDA No. 70-189

-2-

April 1, 1985

We trust that you will find this information satisfactory and that the application may now be considered approvable.

Sincerely,

WYETH LABORATORIES INC.

A handwritten signature in dark ink, appearing to read "Joseph N. Bathish". The signature is fluid and cursive, with a long, sweeping underline.

Joseph N. Bathish
Director, Regulatory Affairs

JNB:tja
Enclosures

RECEIVED

APR 2 1985

GENERIC DRUGS

NDA 70-189

JAN 22 1985

Wyeth Laboratories Inc.
Attention: Joseph N. Bathish
P.O. Box 8290
Philadelphia, PA 19101

Gentlemen:

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

NAME OF DRUG: Naloxone Hydrochloride Injection USP, (Pediatric)
0.02 mg/ml in 2 ml tubex

DATE OF APPLICATION: December 28, 1984

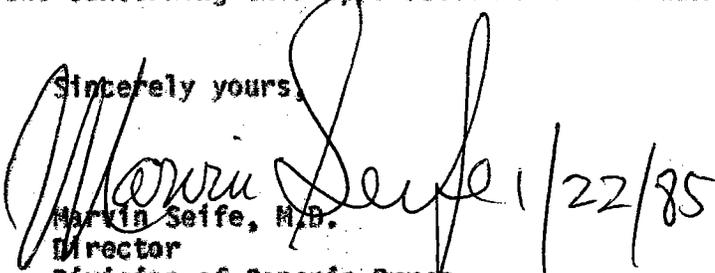
DATE OF RECEIPT: January 3, 1985

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

With future submissions please have the tabs on the back cover of the application on the top - not the bottom.

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

Sincerely yours,

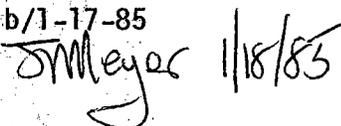

Marvin Seife, M.D.

Director
Division of Generic Drugs
Office of Drug Standards
Center for Drugs and Biologics

PHI-DO DUP HFN-230

JLMeyer/mlb/1-17-85

Ack:
(1471A)


1/18/85