

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-024 / S-036

Trade Name: Nubain Injection

Generic Name: (nalbuphine hydrochloride)

Sponsor: Endo Pharmaceuticals

Approval Date: April 30, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-024 / S-036

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-024 / S-036

APPROVAL LETTER



NDA 18-024/036

Endo Pharmaceuticals Inc.
100 Painters Drive
Chadds Ford, PA 19317

Attention: Ira C. Lentz
Manager, Regulatory Affairs

Dear Mr. Lentz:

Please refer to your supplemental new drug application dated May 6, 1996, received May 7, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nubain (nalbuphine hydrochloride) Injection.

We acknowledge receipt of your submissions dated October 24, 1996, and February 25, 2002. Your submission of February 25, 2002, constituted a complete response to our November 26, 2001, action letter.

Reference is also made to the April 14, 2003, telephone conversation between you and Ms. Parinda Jani of this Division.

This supplemental new drug application provides for extensive labeling changes in the **DESCRIPTION, CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, DRUG ABUSE AND DEPENDENCE, OVERDOSAGE, DOSAGE AND ADMINISTRATION** and **HOW SUPPLIED** sections of the package insert.

We have completed the review of this supplemental application, as amended, and it is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical and include the minor editorial revision indicated, to the draft package insert submitted February 25, 2002. These revisions are terms of the approval of this application.

C J

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 18-024/S-036." Approval of this submission by FDA is not required before the labeling is used.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

If a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to appropriate NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Ms. Lisa Basham-Cruz, Regulatory Health Project Manager, at (301) 827-7410.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Acting Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Bob Rappaport
4/30/03 05:42:26 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-024 / S-036

APPROVABLE LETTER



NDA 18-024/S-036

Endo Pharmaceuticals
223 Wilmington West Chester Pike
Chadds Ford, PA 19317

Attention: Mary Alice Raudenbush
Director, Regulatory Affairs

Dear Ms. Raudenbush:

Please refer to your supplemental new drug application dated May 6, 1996, received May 7, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nubain (nalbuphine hydrochloride) Injection.

We acknowledge receipt of your amendment dated October 24, 1996.

This "Special Supplement-Changes Being Effected" supplement proposes labeling changes in the DESCRIPTION, CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, DRUG ABUSE AND DEPENDENCE, OVERDOSAGE, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED sections of the package insert.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following.

1. Add chemical and physical information to the **DESCRIPTION** section. Include information such as molecular weight, partition coefficient and pKa values at
2. Include the following sentence in the **DESCRIPTION** section.

3. Modify the fourth paragraph of the **CLINICAL PHARMACOLOGY** section as follows.

NUBAIN may produce the same degree of respiratory depression as equianalgesic doses of morphine. However, NUBAIN exhibits a ceiling effect such that increases in dose greater than 30 mg do not produce further respiratory depression in the absence of other CNS active medications affecting respiration.

4. Modify the **WARNINGS Use in Pregnancy (other than labor)** subsection as follows.

Severe fetal bradycardia has been reported when NUBAIN is administered during labor. Naloxone may reverse these effects. Although there are no reports of fetal bradycardia earlier in pregnancy, it is possible that this may occur. This drug should be used in pregnancy only if clearly needed, if the potential benefit outweighs the risk to the fetus, and if appropriate measures such as fetal monitoring are taken to detect and manage any potential adverse effect on the fetus.

5. Modify the **WARNINGS Use During Labor and Delivery** subsection as follows.

The placental transfer of nalbuphine is high, rapid, and variable with a maternal to fetal ratio ranging from 1:0.37 to — fetal and neonatal adverse effects that have been reported following the administration of nalbuphine to the mother during labor include fetal bradycardia, respiratory depression at birth, apnea, cyanosis and hypotonia. Maternal administration of naloxone during labor has normalized these effects in some cases. Severe and prolonged fetal bradycardia has been reported. Permanent neurological damage attributed to fetal bradycardia has occurred. A sinusoidal fetal heart rate pattern associated with the use of nalbuphine has also been reported. NUBAIN should be used during labor and delivery only if clearly indicated and only if the potential benefit outweighs the risk to the infant. Newborns should be monitored for respiratory depression, apnea, bradycardia and arrhythmias if NUBAIN has been used.”

6. Revise the fourth bullet of the **PRECAUTIONS Information for Patients** subsection as follows.

Abrupt discontinuation of NUBAIN after prolonged usage may cause signs and symptoms of withdrawal.

7. Revise the **PRECAUTIONS Laboratory Tests** subsection as follows.

NUBAIN (nalbuphine hydrochloride) may interfere with enzymatic methods for the detection of opioids depending on the specificity/sensitivity of the test. Consult the test manufacturer for specific details.

8. Revise the **PRECAUTIONS Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection as follows.

Carcinogenesis

Long term carcinogenicity studies were performed in rats (24 months) and mice (19 months) by oral administration at doses up to 200 mg/kg (1180 mg/m²) and 200 mg/kg (600 mg/m²) per day, respectively. There was no evidence of an increase in tumors in either species related to NUBAIN administration. The maximum recommended human dose (MRHD) in a day is 160 mg subcutaneously, intramuscularly or intravenously, or approximately 100 mg/m²/day for a 60 kg subject.

Mutagenesis

NUBAIN did not have mutagenic activity in the AMES test with four bacterial strains, in the Chinese Hamster Ovary HGPRT assays or in the Sister Chromatids Exchange Assay. However, NUBAIN induced an increased frequency of mutation in the mouse lymphoma assay. Clastogenic activity was not observed in the mouse micronucleus test of the cytogenicity bone marrow assay in rats.

Impairment of Fertility

A reproduction study was performed in male and female rats at subcutaneous doses up to 56 mg/kg/day or 330 mg/m²/day. NUBAIN did not affect either male or female fertility rates.

9. Revise the **PRECAUTIONS Usage in Pregnancy** subsection as follow.

Teratogenic Effects – Pregnancy Category B

Reproduction studies have been performed in rats by subcutaneous administration of nalbuphine up to 100 mg/kg/day, or 590 mg/m²/day which is approximately 6 times the MRHD, and in rabbits by intravenous administration of nalbuphine up to 32 mg/kg/day, or 378 mg/m²/day which is approximately 4 times the MRHD. The results did not reveal evidence of developmental toxicity, including teratogenicity, 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, this drug should be used during pregnancy only if clearly needed.

Non-Teratogenic Effects

Neonatal body weight and survival rates were reduced at birth and during lactation when nalbuphine was subcutaneously administered to female and male rats prior to mating and throughout gestation and lactation or to pregnant rats during the last third of gestation and throughout lactation at doses approximately 4 times the maximum recommended human dose.

10. Add seizures as one of the adverse drug reactions under the **ADVERSE REACTIONS Post-marketing** subsection.

11. Revise the **DRUG ABUSE AND DEPENDENCE** section as follows.

There have been reports of abuse and dependence associated with Nubain among health care providers, patients and bodybuilders. There have been reported instances of psychological and physical dependence and tolerance in patients abusing NUBAIN. Individuals with a prior history of opioid or other substance abuse or dependence may be at greater risk in responding to reinforcing properties of NUBAIN.

Abrupt discontinuation of NUBAIN following prolonged use has been followed by symptoms of narcotic withdrawal, i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and piloerection.

12. Revise the **OVERDOSAGE** section as follows.

The immediate intravenous administration an opiate antagonist such as naloxone or nalmefene is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

13. Move the sentence "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit." from the **HOW SUPPLIED** section to the **DOSAGE AND ADMINISTRATION** section.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, call Lisa Basham, Regulatory Project Manager, at (301) 827-7420.

Sincerely,

{See appended electronic signature page}

Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Cynthia McCormick
11/26/01 01:30:22 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-024 / S-036

APPROVED LABELING

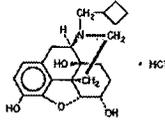


NUBAIN® (Nalbuphine Hydrochloride)

R_x only

DESCRIPTION

NUBAIN (nalbuphine hydrochloride) is a synthetic opioid agonist-antagonist analgesic of the phenanthrene series. It is chemically related to both the widely used opioid antagonist, naloxone, and the potent opioid analgesic, oxycodone. Chemically, nalbuphine hydrochloride is 17-(cyclobutylmethyl)-4,5a-epoxymorphinan-3,6a,14-triol hydrochloride. Nalbuphine hydrochloride molecular weight is 393.61 and is soluble in H₂O (35.5 mg/mL @ 25°C) and ethanol (0.8%); insoluble in CHCl₃ and ether. Nalbuphine hydrochloride has pKa values of 8.71 and 9.96. The molecular formula is C₂₁H₂₇NO₄ · HCl. The structural formula is:



NUBAIN is a sterile solution suitable for subcutaneous, intramuscular, or intravenous injection. NUBAIN is available in two concentrations, 10 mg and 20 mg of nalbuphine hydrochloride per mL. Both strengths in 10 mL vials contain 0.94% sodium citrate dihydrate, 1.26% citric acid anhydrous, and 0.2% of a 9:1 mixture of methylparaben and propylparaben as preservatives; pH is adjusted, if necessary, to 3.5 to 3.7 with hydrochloric acid. The 10 mg/mL strength contains 0.2% sodium chloride.

NUBAIN is also available in ampuls in a sterile, paraben-free formulation in two concentrations, 10 mg and 20 mg of nalbuphine hydrochloride per mL. One mL of each strength contains 0.94% sodium citrate dihydrate, and 1.26% citric acid anhydrous; pH is adjusted, if necessary, to 3.5 to 3.7 with hydrochloric acid. The 10 mg/mL strength contains 0.2% sodium chloride.

CLINICAL PHARMACOLOGY

NUBAIN is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis. Receptor studies show that NUBAIN binds to mu, kappa, and delta receptors, but not to sigma receptors. NUBAIN is primarily a kappa agonist/partial mu antagonist analgesic.

The onset of action of NUBAIN occurs within 2 to 3 minutes after intravenous administration, and in less than 15 minutes following subcutaneous or intramuscular injection. The plasma half-life of nalbuphine is 5 hours, and in clinical studies the duration of analgesic activity has been reported to range from 3 to 6 hours.

The opioid antagonist activity of NUBAIN is one-fourth as potent as nalorphine and 10 times that of pentazocine.

NUBAIN may produce the same degree of respiratory depression as equianalgesic doses of morphine. However, NUBAIN exhibits a ceiling effect such that increases in dose greater than 30 mg do not produce further respiratory depression in the absence of other CNS active medications affecting respiration.

NUBAIN by itself has potent opioid antagonist activity at doses equal to or lower than its analgesic dose. When administered following or concurrent with mu agonist opioid analgesics (e.g., morphine, oxycodone, fentanyl), NUBAIN may partially reverse or block opioid-induced respiratory depression from the mu agonist analgesic. NUBAIN may precipitate withdrawal in patients dependent on opioid drugs. NUBAIN should be used with caution in patients who have been receiving mu opioid analgesics on a regular basis.

INDICATIONS AND USAGE

NUBAIN is indicated for the relief of moderate to severe pain. NUBAIN can also be used as a supplement to balanced anesthesia, for preoperative and postoperative analgesia, and for obstetrical analgesia during labor and delivery.

CONTRAINDICATIONS

NUBAIN should not be administered to patients who are hypersensitive to nalbuphine hydrochloride, or to any of the other ingredients in NUBAIN.

WARNINGS

NUBAIN should be administered as a supplement to general anesthesia only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

Naloxone, resuscitative and intubation equipment and oxygen should be readily available.

Drug Abuse

Caution should be observed in prescribing NUBAIN for emotionally unstable patients, or for individuals with a history of opioid abuse. Such patients should be closely supervised when long-term therapy is contemplated (see DRUG ABUSE AND DEPENDENCE).

Use in Ambulatory Patients

NUBAIN may impair the mental or physical abilities required for the performance of potentially dangerous tasks, such as driving a car or operating machinery. Therefore, NUBAIN should be administered with caution to ambulatory patients who should be warned to avoid such hazards.

Use in Emergency Procedures

Maintain patient under observation until recovered from NUBAIN effects that would affect driving or other potentially dangerous tasks.

Use in Pregnancy (Other Than Labor)

Severe fetal bradycardia has been reported when NUBAIN is administered during labor. Naloxone may reverse these effects. Although there are no reports of fetal bradycardia earlier in pregnancy, it is possible that this may occur. This drug should be used in pregnancy only if clearly needed, if the potential benefit outweighs the risk to the fetus, and if appropriate measures such as fetal monitoring are taken to detect and manage any potential adverse effect on the fetus.

Use During Labor and Delivery

The placental transfer of nalbuphine is high, rapid, and variable with a maternal to fetal ratio ranging from 1.0:37 to 1:6. Fetal and neonatal adverse effects that have been reported following the administration of nalbuphine to the mother during labor include fetal bradycardia, respiratory depression at birth, apnea, cyanosis and hypotonia. Maternal administration of naloxone during labor has normalized these effects in some cases. Severe and prolonged fetal bradycardia has been reported. Permanent neurological damage attributed to fetal bradycardia has occurred. A sinusoidal fetal heart rate pattern associated with the use of nalbuphine has also been reported. NUBAIN should be used during labor and delivery only if clearly indicated and only if the potential benefit outweighs the risk to the infant. Newborns should be monitored for respiratory depression, apnea, bradycardia, and arrhythmias if NUBAIN has been used.

Head Injury and Increased Intracranial Pressure

The possible respiratory depressant effects and the potential of potent analgesics to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO₂ retention) may be markedly exaggerated in the presence of head injury, intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, potent analgesics can produce effects which may obscure the clinical course of patients with head injuries. Therefore, NUBAIN should be used in these circumstances only when essential, and then should be administered with extreme caution.

Interaction with Other Central Nervous System Depressants

Although NUBAIN possesses opioid antagonist activity, there is evidence that in nondependent patients it will not antagonize an opioid analgesic administered just before, concurrently, or just after an injection of NUBAIN. Therefore, patients receiving an opioid analgesic, general anesthetics, phenothiazines, or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUBAIN may exhibit an additive effect. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

PRECAUTIONS

General

Impaired Respiration: At the usual adult dose of 10 mg/70 kg, NUBAIN causes some respiratory depression approximately equal to that produced by equal doses of morphine. However, in contrast to morphine, respiratory depression is not appreciably increased with higher doses of NUBAIN. Respiratory depression induced by NUBAIN can be reversed by NARCAN® (naloxone hydrochloride) when indicated. NUBAIN should be administered with caution at low doses to patients with impaired respiration (e.g., from other medication, uremia, bronchial asthma, severe infection, cyanosis, or respiratory obstructions).

Impaired Renal or Hepatic Function: Because NUBAIN is metabolized in the liver and excreted by the kidneys, NUBAIN should be used with caution in patients with renal or liver dysfunction and administered in reduced amounts.

Myocardial Infarction: As with all potent analgesics, NUBAIN should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Tract Surgery: As with all opioid analgesics, NUBAIN should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

Cardiovascular System: During evaluation of NUBAIN in anesthesia, a higher incidence of bradycardia has been reported in patients who did not receive atropine pre-operatively.

Information for Patients

Patients should be advised of the following information:

- NUBAIN is associated with sedation and may impair mental and physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery.
- NUBAIN is to be used as prescribed by a physician. Dose or frequency should not be increased without first consulting with a physician since NUBAIN may cause psychological or physical dependence.
- The use of NUBAIN with other opioids can cause signs and symptoms of withdrawal.
- Abrupt discontinuation of NUBAIN after prolonged usage may cause signs and symptoms of withdrawal.

Laboratory Tests

NUBAIN may interfere with enzymatic methods for the detection of opioids depending on the specificity/sensitivity of the test. Consult the test manufacturer for specific details.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long term carcinogenicity studies were performed in rats (24 months) and mice (19 months) by oral administration at doses up to 200 mg/kg (1160 mg/m²) and 200 mg/kg (600 mg/m²) per day, respectively. There was no evidence of an increase in tumors in either species related to NUBAIN administration. The maximum recommended human dose (MRHD) in a day is 160 mg subcutaneously, intramuscularly or intravenously, or approximately 100 mg/m²/day for a 60 kg subject.

Mutagenesis

NUBAIN did not have mutagenic activity in the AMES test with four bacterial strains, in the Chinese Hamster Ovary HGPRT assays or in the Sister Chromatid Exchange Assay. However, NUBAIN induced an increased

frequency of mutation in the mouse lymphoma assay. Clastogenic activity was not observed in the mouse micronucleus test of the cytogenically bone marrow assay in rats.

Impairment of Fertility

A reproduction study was performed in male and female rats at subcutaneous doses up to 56 mg/kg/day or 330 mg/m²/day. NUBAIN did not affect either male or female fertility rats.

Usage in Pregnancy

Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats by subcutaneous administration of nalbuphine up to 100 mg/kg/day, or 590 mg/m²/day which is approximately 6 times the MRHD, and in rabbits by intravenous administration of nalbuphine up to 32 mg/kg/day, or 378 mg/m²/day which is approximately 4 times the MRHD. The results did not reveal evidence of developmental toxicity, including teratogenicity, 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, this drug should be used during pregnancy only if clearly needed.

Non-teratogenic Effects: Neonatal body weight and survival rates were reduced at birth and during lactation when nalbuphine was subcutaneously administered to female and male rats prior to mating and throughout gestation and lactation or to pregnant rats during the last third of gestation and throughout lactation at doses approximately 4 times the maximum recommended human dose.

Use During Labor and Delivery

See WARNINGS.

Nursing Mothers

Limited data suggest that NUBAIN is excreted in maternal milk but only in a small amount (less than 1% of the administered dose) and with a clinically insignificant effect. Caution should be exercised when NUBAIN is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

ADVERSE REACTIONS

The most frequent adverse reaction in 1066 patients treated in clinical studies with NUBAIN was sedation 381 (36%).

Less frequent reactions were: sweaty/dampy 90 (9%), nausea/vomiting 68 (6%), dizziness/vertigo 58 (5%), dry mouth 44 (4%), and headache 27 (3%).

Other adverse reactions which occurred (reported incidence of 1% or less) were:

CNS Effects: Nervousness, depression, restlessness, crying, euphoria, floating, hostility, unusual dreams, confusion, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality. The incidence of psychomimetic effects, such as unreality, depersonalization, delusions, dysphoria and hallucinations has been shown to be less than that which occurs with pentazocine.

Cardiovascular: Hypertension, hypotension, bradycardia, tachycardia.

Gastrointestinal: Cramps, dyspepsia, bitter taste.

Respiratory: Depression, dyspnea, asthma.

Dermatologic: Itching, burning, urticaria.

Miscellaneous: Speech difficulty, urinary urgency, blurred vision, flushing and warmth.

Allergic Reactions: Anaphylactic/anaphylactoid and other serious hypersensitivity reactions have been reported following the use of nalbuphine and may require immediate, supportive medical treatment. These reactions may include shock, respiratory distress, respiratory arrest, bradycardia, cardiac arrest, hypotension, or laryngeal edema. Other allergic-type reactions reported include stidor, bronchospasm, wheezing, edema, rash, pruritus, nausea, vomiting, diaphoresis, weakness, and shakiness.

Post-marketing: Other reports include pulmonary edema, agitation, seizures, and injection site reactions such as pain, swelling, redness, burning, and hot sensations.

DRUG ABUSE AND DEPENDENCE

There have been reports of abuse and dependence associated with NUBAIN among health care providers, patients and bodybuilders. There have been reported instances of psychological and physical dependence and tolerance in patients abusing NUBAIN. Individuals with a prior history of opioid or other substance abuse or dependence may be at greater risk in responding to reinforcing properties of NUBAIN.

Abrupt discontinuation of NUBAIN following prolonged use has been followed by symptoms of opioid withdrawal, i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and piloerection.

OVERDOSAGE

The immediate intravenous administration of an opiate antagonist such as naloxone or nalmefene is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

The administration of single doses of 72 mg of NUBAIN subcutaneously to eight normal subjects has been reported to have resulted primarily in symptoms of sleepiness and mild dysphoria.

DOSAGE AND ADMINISTRATION

The usual recommended adult dose is 10 mg for a 70 kg individual, administered subcutaneously, intramuscularly or intravenously; this dose may be repeated every 3 to 6 hours as necessary. Dosage should be

adjusted according to the severity of the pain, physical status of the patient, and other medications which the patient may be receiving. (See Interaction with Other Central Nervous System Depressants under WARNINGS). In non-tolerant individuals, the recommended single maximum dose is 20 mg, with a maximum total daily dose of 150 mg.

The use of NUBAIN as a supplement to balanced anesthesia requires larger doses than those recommended for analgesia. Induction doses of NUBAIN range from 0.3 mg/kg to 3 mg/kg intravenously to be administered over a 10 to 15 minute period with maintenance doses of 0.25 to 0.5 mg/kg in single intravenous administrations as required. The use of NUBAIN may be followed by respiratory depression which can be reversed with the opioid antagonist NARCAN® (naloxone hydrochloride).

NUBAIN is physically incompatible with naloxone and ketorolac.

Patients Dependent on Opioids

Patients who have been taking opioids chronically may experience withdrawal symptoms upon the administration of NUBAIN. If untidy troublesome, opioid withdrawal symptoms can be controlled by the slow intravenous administration of small increments of morphine, until relief occurs. If the previous analgesic was morphine, meperidine, codeine, or other opioid with similar duration of activity, one-fourth of the anticipated dose of NUBAIN can be administered initially and the patient observed for signs of withdrawal, i.e., abdominal cramps, nausea and vomiting, lacrimation, rhinorrhea, anxiety, restlessness, elevation of temperature or piloerection. If untoward symptoms do not occur, progressively larger doses may be tried at appropriate intervals until the desired level of analgesia is obtained with NUBAIN.

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

HOW SUPPLIED

NUBAIN® (nalbuphine hydrochloride) injection for intramuscular, subcutaneous, or intravenous use is a sterile solution available in:

NDC 63481-608-05 (sulfite-free) 10 mg/mL, 10 mL multiple dose vials (box of 1)
NDC 63481-432-10 (sulfite/paraben-free) 10 mg/mL, 1 mL ampuls (box of 10)
NDC 63481-609-05 (sulfite-free) 20 mg/mL, 10 mL multiple dose vials (box of 1)
NDC 63481-433-10 (sulfite/paraben-free) 20 mg/mL, 1 mL ampuls (box of 10)

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.] Protect from excessive light. Store in carton until contents have been used.

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317



Manufactured by:
Bristol-Myers Squibb Holdings Pharma, Ltd.
Manati, Puerto Rico 00674 USA

NUBAIN® is a Registered Trademark of Endo Pharmaceuticals Inc.
NARCAN® is a Registered Trademark of Endo Pharmaceuticals Inc.

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51-022542-00/May, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-024 / S-036

MEDICAL REVIEW

NDA: 18-024

SERIAL: S-036

NAME: Nubain® (nalbuphine hydrochloride)

SPONSOR: Endo Pharmaceuticals Inc.

SUBMISSION DATE: May 6, 1996, Oct 24, 1996, Feb 25, 2002

RECEIPT DATE: May 7, 1996, Oct 29, 1996, Feb 27, 2002

REVIEW DATE: Mar 19, 2003

TYPE OF SUBMISSION: Label supplement

REVIEWER: Howard Josefberg, MD

SUPERVISORY PROJECT MANAGER: Parinda Jani

Background:

Nubain® (nalbuphine hydrochloride), originally approved in 1979, has undergone several label revisions since. The most recent (Special Supplement- Changes Being Effected, #36) was submitted in May, 1996. In November, 2001 the sponsor received an Approvable letter, and was asked to revise the proposed label in order to fully comply with 21 CFR 314.70(b), and to take into account all available safety information. The Agency requested a number of specific changes in label wording. The revised label was then resubmitted February 25, 2002 (#036). Parinda Jani, Chief of HFD-170's Project Management staff, has written the detailed Label Review. This review has been excerpted from Ms. Jani's except for the clinical review comments under the DRUG ABUSE AND DEPENDENCE section,

1. HEADER section:

There are no changes made to this section.

2. DESCRIPTION section:

As requested the sponsor has revised the DESCRIPTION section to include chemical and physical information such as chemical name, molecular weight and formula and partition coefficient. _____ e following

[]

3. CLINICAL PHARMACOLOGY section:

As requested the fourth paragraph of the CLINICAL PHARMACOLOGY section has been revised as follows:

“NUBAIN may produce the same degree of respiratory depression as equianalgesic doses of morphine. However, NUBAIN exhibits a ceiling effect such that increases in dose greater than 30 mg do not produce further respiratory depression in the absence of other CNS active medications affecting respiration.”

4. INDICATIONS AND USAGE section:

There are no changes made to this section.

5. CONTRAINDICATIONS section:

There are no changes made to this section.

6. WARNINGS section:

As requested the **Use in Pregnancy (other than labor)** subsection has been revised as follows:

“Severe fetal bradycardia has been reported when NUBAIN is administered during labor. Naloxone may reverse these effects. Although there are no reports of fetal bradycardia earlier in pregnancy, it is possible that this may occur. This drug should be used in pregnancy only if clearly needed, if the potential benefit outweighs the risk to the fetus, and if appropriate measures such as fetal monitoring are taken to detect and manage any potential adverse effect on the fetus.”

As requested the **Use During Labor and Delivery** subsection has been revised as follows:

“The placental transfer of nalbuphine is high, rapid, and variable with a maternal to fetal ratio ranging from 1:0.37 to 1:1. Fetal and neonatal adverse effects that have been reported following the administration of nalbuphine to the mother during labor include fetal bradycardia, respiratory depression at birth, apnea, cyanosis and hypotonia. Maternal administration of naloxone during labor has normalized these effects in some cases. Severe and prolonged fetal bradycardia has been reported. Permanent neurological damage attributed to fetal bradycardia has occurred. A sinusoidal fetal heart rate pattern associated with the use of nalbuphine has also been reported. NUBAIN should be used during labor and delivery only if clearly indicated and only if the potential benefit outweighs the risk to the infant. Newborns should be monitored for respiratory depression, apnea, bradycardia and arrhythmias if NUBAIN has been used.”

In addition the sponsor has corrected the maternal to fetal ratio ranging from "1:0.37 to 1:6". The sponsor has included references to support this change.

As requested the fourth bullet of the **Information for Patients** subsection has been revised as follows:

"Abrupt discontinuation of NUBAIN after prolonged usage may cause signs and symptoms of withdrawal."

As requested the **Laboratory Tests** subsection has been revised as follows:

"NUBAIN (nalbuphine hydrochloride) may interfere with enzymatic methods for the detection of opioids depending on the specificity/sensitivity of the test. Consult the test manufacturer for specific details."

As requested the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsections have been revised as follows:

Carcinogenesis

"Long term carcinogenicity studies were performed in rats (24 months) and mice (19 months) by oral administration at doses up to 200 mg/kg (1180 mg/m²) and 200 mg/kg (600 mg/m²) per day, respectively. There was no evidence of an increase in tumors in either species related to NUBAIN administration. The maximum recommended human dose (MRHD) in a day is 160 mg subcutaneously, intramuscularly or intravenously, or approximately 100 mg/m²/day for a 60 kg subject."

Mutagenesis

"NUBAIN did not have mutagenic activity in the AMES test with four bacterial strains, in the Chinese Hamster Ovary HGPRT assays or in the Sister Chromatids Exchange Assay. However, NUBAIN induced an increased frequency of mutation in the mouse lymphoma assay. Clastogenic activity was not observed in the mouse micronucleus test of the cytogenicity bone marrow assay in rats."

Impairment of Fertility

"A reproduction study was performed in male and female rats at subcutaneous doses up to 56 mg/kg/day or 330 mg/m²/day. NUBAIN did not affect either male or female fertility rates."

7. PRECAUTIONS section:

As requested the **Usage in Pregnancy** subsection has been revised as follows:

"Teratogenic Effects – Pregnancy Category B

Reproduction studies have been performed in rats by subcutaneous administration of nalbuphine up to 100 mg/kg/day, or 590 mg/m²/day which is approximately 6 times the MRHD, and in rabbits by intravenous administration of nalbuphine up to 32 mg/kg/day, or 378 mg/m²/day which is approximately 4 times the MRHD. The results did not reveal evidence of developmental toxicity, including teratogenicity, 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, this drug should be used during pregnancy only if clearly needed.”

Non-Teratogenic Effects

Neonatal body weight and survival rates were reduced at birth and during lactation when nalbuphine was subcutaneously administered to female and male rats prior to mating and throughout gestation and lactation or to pregnant rats during the last third of gestation and throughout lactation at doses approximately 4 times the maximum recommended human dose.”

8. ADVERSE REACTIONS section:

As requested “seizures” is added as one of the adverse drug reactions under the **Post-Marketing** subsection.

9. DRUG ABUSE AND DEPENDENCE section:

As requested this section has been revised as follows:

“There have been reports of abuse and dependence associated with NUBAIN among health care providers, patients and bodybuilders. There have been reported instances of psychological and physical dependence and tolerance in patients abusing NUBAIN. Individuals with a prior history of opioid or other substance abuse or dependence may be at greater risk in responding to reinforcing properties of NUBAIN.”

“Abrupt discontinuation of NUBAIN following prolonged use has been followed by symptoms of narcotic withdrawal, i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and piloerection.”

Clinical Review Comments:

The sponsor was asked to address the issue of Nubain[®] abuse in bodybuilders because of a series of 13 AEs in bodybuilders, reported in the May, 1996 Special Supplement/label revision. Nubain[®] abuse in bodybuilders has also been reported in several small case series published in sports medicine and addiction medicine journals (Wines JD, *et al*, 1999, American Journal of Addiction; McBride AJ, *et al*, 1996, British Journal of Sports Medicine). In their 1999 article Wines, *et al* interviewed 11 nalbuphine using bodybuilders, 8 of whom they classified as clinically dependent on the drug. Several subjects reported (incorrect) expectations of physiologic benefit. Others said that it enabled them to train harder and cope with the resulting pain, or that it helped reduce pain from injections of steroids and other illicit substances integral to their muscle building routines.

Many references to Nubain[®] use also appear in the lay “bodybuilding literature,” widely available now via the internet. “The Underground Steroid Handbook” (Duchaine, 1988) first proposed in (published) print, the use of Nubain[®] for muscle enhancement, based on

the false premise that the drug lowers cortisol levels, resulting in faster recovery after a weight lifting session and improved muscle growth. Meanwhile, studies from the addiction medicine literature report a subset of steroid injecting bodybuilders meet criteria for recreational substance abuse disorders. Nubain[®], unscheduled under the Controlled Substances Act, was widely available in bodybuilding circles, and considered part of the bodybuilder's arsenal, sometimes for improving muscle mass, other times for recreation. The inclusion of this particular warning is warranted.

10. OVERDOSAGE section:

As requested this section is revised as follows:

“The immediate intravenous administration an opiate antagonist such as naloxone or nalmefene is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.”

11. DOSAGE AND ADMINISTRATION and HOW SUPPLIED section:

As requested the sentence “Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.” Is moved from the HOW SUPPLIED section to the DOSAGE AND ADMINISTRATION section.

Recommendations and Conclusions

The proposed label is now in accordance with 21 CFR 314.70(b) and includes the most recently available safety information. The inclusion of a specific warning concerning Nubain[®] abuse in bodybuilders in the DRUG ABUSE AND DEPENDENCE section is warranted. The proposed label will be acceptable.

Howard Josefberg, MD
Medical Officer

Sharon Hertz, MD
Team Leader

CC: Division File
Original NDA
B.A. Rappaport, MD
Project Manager: Parinda Jani

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this page is the manifestation of the electronic signature.**

/s/

Howard Josefberg
3/25/03 12:17:21 PM
MEDICAL OFFICER

Sharon Hertz
3/27/03 02:49:37 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-024 / S-036

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE



NDA 18-024/S-036

Endo Pharmaceuticals Inc.
100 Painters Drive
Chadds Ford, PA 19317

Attention: Ira C. Lentz
Manager, Regulatory Affairs

Dear Mr. Lentz:

We acknowledge receipt of your May 30, 2003, submission containing final printed labeling in response to our April 30, 2003, letter approving your supplemental new drug application for Nubain (nalbuphine hydrochloride) Injection.

We have reviewed the labeling that you submitted in accordance with our April 30, 2003, letter and we find it acceptable.

If you have any questions, call Lisa Basham-Cruz, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Parinda Jani
8/1/03 08:46:58 AM

Division of Anesthetics, Critical care, and Addiction Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 18-024/S-036
Name of Drug: Nubain (nalbuphine hydrochloride)
Sponsor: Endo Laboratories

Material Reviewed

Submission date(s): May 6 and October 24, 1996, and February 25, 2002
Receipt Date(s): May 7 and October 29, 1996, and February 27, 2002

Background and Summary description: In accordance with the requirements of 21 CFR 314.70(b), this supplement provides for major revisions to the **DESCRIPTION, CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS,** and the **DRUG ABUSE AND DEPENDENCE** sections.

Also refer to the RPM review dated November 23, 2001, and the Agency's approvable letter dated November 26, 2001. In addition to the changes listed in the RPM review dated, November 23, 2001, the sponsor has incorporated the changes listed in the approvable letter dated November 26, 2001. In cases where it was not feasible to revise the labeling, the sponsor has provided justification.

Status Report

Reviews Completed: Tim McGovern: Pharm/tox TL (no comments), Suresh Doddapaneni; Clin/Pharl TL (no comments), Howard Josefberg: Clinical review in DFS (recommendation-approval), Pat Maturu: CMC (see the comment below in the DESCRIPTION section)

Reviews Pending: None.

RPM REVIEW

Please note that a strikethrough indicates deletion and an underline indicates addition to the approved label.

Throughout the labeling the sponsor has replaced the term "narcotic" with "opioid".

HEADER: There are no changes made to this section.

BOX WARNING: Not applicable.

DESCRIPTION:

As requested by the Agency, the sponsor has revised the **DESCRIPTION** section to include chemical and physical information such as chemical name, molecular weight, molecular formula, partition coefficient and p

at a temperature of 37°C. Also, a statement regarding the structural activity relationships is included.

The first paragraph is revised as follows:

“NUBAIN (nalbuphine hydrochloride) is a synthetic opioid agonist-antagonist analgesic of the phenanthrene series. It is chemically related to both the widely used opioid antagonist, naloxone, and the potent opioid analgesic, oxycodone. Chemically nalbuphine hydrochloride is 17-(cyclobutylmethyl)-4,5-epoxymorphinan-3,6,14-triol hydrochloride. Nalbuphine hydrochloride molecular weight is 393.91 and is soluble in H₂O (35.5 mg/mL @ 25°C) and ethanol (0.8%); insoluble in CHCl₃ and ether. Nalbuphine hydrochloride has pKa values of 8.71 and 9.96. The molecular formula is C₂₁H₂₇NO₄ · HCl. The structural formula is:”

[

]

CLINICAL PHARMACOLOGY:

As requested by the Agency, the fourth paragraph of the **CLINICAL PHARMACOLOGY** section is modified as follows.

“NUBAIN may produce the same degree of respiratory depression as equianalgesic doses of morphine. However, NUBAIN exhibits a ceiling effect such that increases in dose greater than 30 mg do not produce further respiratory depression in the absence of other CNS active medications affecting respiration.”

INDICATION AND USAGE: There are no changes made to this section.

CONTRAINDICATIONS: There are no changes made to this section.

WARNINGS:

As requested by the Agency, the **Use in Pregnancy** (other than labor) subsection is revised as follows.

“Severe fetal bradycardia has been reported when NUBAIN is administered during labor. Naloxone may reverse these effects. Although there are no reports of fetal bradycardia earlier in pregnancy, it is possible that this may occur. This drug should be used in pregnancy only if clearly needed, if the potential benefit outweighs the risk to the fetus, and if appropriate measures such as fetal monitoring are taken to detect and manage any potential adverse effect on the fetus.”

As requested by the Agency, the **Use During Labor and Delivery** subsection is revised as follows.

“The placental transfer of nalbuphine is high, rapid, and variable with a maternal to fetal ratio ranging from 1:0.37 to — Fetal and neonatal adverse effects that have been reported following the administration of nalbuphine to the mother during labor include fetal bradycardia,

respiratory depression at birth, apnea, cyanosis and hypotonia. Maternal administration of naloxone during labor has normalized these effects in some cases. Severe and prolonged fetal bradycardia has been reported. Permanent neurological damage attributed to fetal bradycardia has occurred. A sinusoidal fetal heart rate pattern associated with the use of nalbuphine has also been reported. NUBAIN should be used during labor and delivery only if clearly indicated and only if the potential benefit outweighs the risk to the infant. Newborns should be monitored for respiratory depression, apnea, bradycardia and arrhythmias if NUBAIN has been used."

In addition, the sponsor has corrected the maternal to fetal ratio ranging from "1:0.37 to 1:0.37 to 1:6". The sponsor has included the reference to support this change (Reference Wilson SJ, Errick K, Balkon J. Pharmacokinetics of Nalbuphine During Parturition. Am J Obstet Gynecol 1986; 155; 2; 340-344). This information was reviewed by Dr. Doddapaneni, and the revision is acceptable

PRECAUTIONS:

As requested by the Agency, the fourth bullet of the **Information for Patients** subsection is revised as follows.

"Abrupt discontinuation of NUBAIN after prolonged usage may cause signs and symptoms of withdrawal."

As requested by the Agency, the **Laboratory Tests** subsection is revised as follows.

"NUBAIN (nalbuphine hydrochloride) may interfere with enzymatic methods for the detection of opioids depending on the specificity/sensitivity of the test. Consult the test manufacture for specific details."

As requested by the Agency, the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection is revised as follows.

Carcinogenesis

Long term carcinogenicity studies were performed in rats (24 months) and mice (19 months) by oral administration at doses up to 200 mg/kg (1180 mg/m²) and 200 mg/kg (600 mg/m²) per day, respectively. There was no evidence of an increase in tumors in either species related to NUBAIN administration. The maximum recommended human dose (MRHD) in a day is 160 mg subcutaneously, intramuscularly or intravenously, or approximately 100 mg/m²/day for a 60 kg subject.

Mutagenesis

NUBAIN did not have mutagenic activity in the AMES test with four bacterial strains, in the Chinese Hamster Ovary HGPRT assays or in the Sister Chromatids Exchange Assay. However, NUBAIN induced an increased frequency of mutation in the mouse lymphoma assay. Clastogenic activity was not observed in the mouse micronucleus test of the cytogenicity bone marrow assay in rats.

Impairment of Fertility

A reproduction study was performed in male and female rats at subcutaneous doses up to 56 mg/kg/day or 330 mg/m²/day. NUBAIN did not affect either male or female fertility rats.

As requested by the Agency, the **Usage in Pregnancy** subsection is revised as follows:

Teratogenic Effects – Pregnancy Category B

Reproduction studies have been performed in rats by subcutaneous administration of nalbuphine up to 100 mg/kg/day, or 590 mg/m²/day which is approximately 6 times the MRHD, and in

rabbits by intravenous administration of nalbuphine up to 32 mg/kg/day, or 378 mg/m²/day which is approximately 4 times the MRHD. The results did not reveal evidence of developmental toxicity, including teratogenicity, or harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant woman. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-Teratogenic Effects

Neonatal body weight and survival rates were reduced at birth and during lactation when nalbuphine was subcutaneously administered to female and male rats prior to mating and throughout gestation and lactation or to pregnant rats during the last third of gestation and throughout lactation at doses approximately 4 times the maximum recommended human dose.

ADVERSE REACTIONS:

As requested by the Agency, "seizures" is added as one of the adverse drug reactions under the **Post-marketing** subsection.

DRUG ABUSE AND DEPENDENCE:

As requested by the Agency, this section is revised as follows.

"There have been reports of abuse and dependence associated with Nubain among health care providers, patients and bodybuilders. There have been reported instances of psychological and physical dependence and tolerance in patients abusing NUBAIN. Individuals with a prior history of opioid or other substance abuse or dependence may be at greater risk in responding to reinforcing properties of NUBAIN. Abrupt discontinuation of NUBAIN following prolonged use has been followed by symptoms of narcotic withdrawal, i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and piloerection."

OVERDOSAGE

As requested by the Agency, this section is revised as follows.

"The immediate intravenous administration an opiate antagonist such as naloxone or nalmefene is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated."

DOSAGE AND ADMINISTRATION and HOW SUPPLIED:

The sentence "Parental drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit." Is moved from the HOW SUPPLIED section to the DOSAGE AND ADMINISTRATION section.

RECOMMENDATIONS

Parinda Jani, Chief, project Management Staff

Bob Rappaport, M.D.

Acting Director, Division of Anesthetics, Critical care, and Addiction Drug products

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Parinda Jani
4/22/03 02:35:10 PM
CSO

Division of Anesthetic, Critical Care, and Addiction Drug Products

PROJECT MANAGER REVIEW

Application Number: NDA 18-024/S-036
Name of Drug: Nubain® (nalbuphine hydrochloride)
Sponsor: Endo Laboratories
CSO: Laura Governale

Material Reviewed

Submission	Compared With
SLR-036 dated May 6, 1996, received May 7, 1996. This supplement provides for major revisions to the DESCRIPTION, CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and the DRUG ABUSE AND DEPENDENCE sections.	FPL for SLR-032 approved on November 2, 1994.

Background and Summary Description:

In accordance with 21 CFR 314.70(b), the sponsor submitted labeling supplement SLR-036 on May 6, 1996.

Status Report

Reviews Completed: SLR-036 label review – October 17, 2000

Project Manager Review

Please note that the sponsor's proposed revisions are indicated by strikeovers and underlined text. The agency's proposed revisions will be bolded.

BOX WARNING: N/A

DESCRIPTION: The firm modified the second and third paragraph of the **DESCRIPTION** section to the following.

“NUBAIN is a sterile solution suitable for subcutaneous, intramuscular, or intravenous injection. NUBAIN is available in two concentrations, 10 mg and 20 mg of nalbuphine hydrochloride per mL. Both strength in 10 mL vials contain 0.94% sodium citrate hydrous, 1.26% citric acid anhydrous, ~~0.1% sodium metabisulfite~~, and 0.2% of 9:1 mixture of methylparaben and propylparaben as preservatives; pH is adjusted, if necessary, to 3.5 to 3.7 with hydrochloric acid. The 10 mg/mL strength contains ~~0.1%~~ 0.2% sodium chloride.

“NUBAIN is also available ~~in as sulfite and~~ in ampules in a sterile, paraben-free formulation in two concentrations, 10 mg and 20 mg of nalbuphine hydrochloride per mL. One mL of each strength contains 0.94% sodium citrate hydrous, and 1.26% citric acid anhydrous; pH is adjusted, if necessary, to 3.5 to 3.7 with hydrochloric acid. The 10 mg/mL strength contains 0.2% sodium chloride.”

See supplement S-035 for information related to these changes/C.Schumaker-11-23-01.

Added by C.Schumaker/11-23-01.

The October 24, 1996, amendment to this supplement contains agreements regarding changes requested in telephone conversations dated October 21 and 23, 1996 (I cannot locate documentation of the conversations./CS 11-23-01) Include changes 1, 3 and 4 in the approvable letter.

1. Add chemical and physical information to the DESCRIPTION section such as molecular weight, partition coefficient and pKa values at degrees.
2. List nalbuphine HCl in the DESCRIPTION section.....using one of two USAN names for the compound. (The company agreed to use the second name in the amendment, but note that the correct name is employed in the May 6, 1996, submission.)
3. Address the structural activity of the alpha and beta epimers of nalbuphine hydrochloride by including the following sentence in the DESCRIPTION section of the package insert ‘

’
4. Please relocate the paragraph “Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.” From the HOW SUPPLIED section to the DOSAGE AND ADMINISTRATION section.

CLINICAL PHARMACOLOGY: The firm modified the title of this section from **ACTIONS** to **CLINICAL PHARMACOLOGY** and made the following revisions to this section.

“NUBAIN is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis. Receptor studies show that NUBAIN binds to mu, kappa, and delta receptors, but not to sigma receptors. NUBAIN is primarily a kappa agonist/partial mu antagonist analgesic.

The onset of action of NUBAIN occurs within 2 to 3 minutes after intravenous administration, and in less than 15 minutes following subcutaneous or intramuscular injection. The plasma half-life of nalbuphine is 5 hours, and in clinical studies the duration of analgesic activity has been reported to range from 3 to 6 hours.

The narcotic antagonist activity of NUBAIN is one-fourth as potent as nalorphine and 10 times that of pentazocine.

NUBAIN may produce the same degree of respiratory depression as equianalgesic doses of morphine. However, NUBAIN exhibits a ceiling effect such that increases in dose greater than 30 mg do not produce further respiratory depression in the absence of other CNS active medications affecting respiration.

NUBAIN by itself has potent narcotic antagonist activity at doses equal to or lower than its analgesic dose. When administered following or concurrent with mu agonist opioid analgesics (e.g., morphine, oxymorphone, fentanyl), NUBAIN may partially reverse or block narcotic-induced respiratory depression from the mu agonist analgesic. NUBAIN may precipitate withdrawal in patients dependent on opioid analgesics

INDICATIONS AND USAGE: The firm revised the title of this section from **INDICATIONS** to **INDICATIONS and USAGE**.

CONTRAINDICATIONS:

The firm revised the following sentence to read:

“NUBAIN should not be administered to patients who are hypersensitive to nalbuphine hydrochloride or to any of the ingredients in NUBAIN.”

WARNINGS: The subsection entitled, **Drug Dependence** was moved to the **DRUG ABUSE AND DEPENDENCE** section and replaced with the following.

“**Drug Abuse** Caution should be observed in prescribing NUBAIN for emotionally unstable patients, or for individuals with a history of

Such patients should be closely supervised when long-term therapy is contemplated (see **DRUG ABUSE AND DEPENDENCE**)”

The firm deleted the subsection entitled **Use in Children**.

~~“**Use in Children**—Clinical experience to support administration to patients under 18 years is not available at present.”~~

The firm modified the last sentence in the following sub-section.

~~“**Use in Pregnancy (other than labor)** Safe use of NUBAIN in pregnancy has not been established. Although animal reproductive studies have not revealed teratogenic or embryotoxic effects, nalbuphine should ~~only~~ be administered to pregnant women ~~when, in the judgement of their physician, the potential benefits outweigh the possible hazards.~~ only if clearly needed.”~~

The Agency proposes to modify the above section to the following.

“Use in Pregnancy (other than labor) Severe fetal bradycardia has been reported when NUBAIN is administered during labor. Naloxone may reverse these effects. Although there are no reports of fetal bradycardia earlier in pregnancy, it is possible that this may occur. This drug should be used in pregnancy only if clearly needed, if the potential benefit outweighs the risk to the fetus, and if appropriate measures such as fetal monitoring are taken to detect and manage any potential adverse effect on the fetus.”

The firm revised the subsection entitled **Use During Labor and Delivery** in the following manner.

SLR-032 (Approved)	SLR-036
<p>“Use During Labor and Delivery NUBAIN can produce respiratory depression and cardiac rhythm disturbances in the neonate. It should be used with caution in women during labor and delivery, and newborns should be monitored for respiratory depression, apnea, bradycardia and arrhythmias if NUBAIN has been used.”</p>	<p>“Use During Labor and Delivery <u>The placental transfer of nalbuphine is high, rapid, and variable with a maternal to fetal ratio ranging from 1:0.37 to —. Fetal and neonatal adverse effects that have been reported following the administration of nalbuphine to the mother during labor include fetal bradycardia, respiratory depression at birth, apnea, cyanosis and hypotonia. Maternal administration of naloxone during labor has normalized these effects in some cases. Severe and prolonged fetal bradycardia has been reported. Permanent neurological damage</u></p>

	<p>attributed to fetal bradycardia has occurred. <u>A sinusoidal fetal heart rate pattern associated with the use of nalbuphine has also been reported. NUBAIN should be used during labor and delivery only if clearly indicated and only if the potential benefit outweighs the risk to the infant. with caution in women during labor and delivery, and nNewborns should be monitored for respiratory depression, apnea, bradycardia and arrhythmias if NUBAIN has been used.”</u></p>
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The firm removed the ~~Sulfite Sensitivity~~ warning from the **WARNINGS** section of the label.

PRECAUTIONS: The firm inserted the header General before the subsection Impaired Respiration.

The firm inserted the established name in the first sentence.

“Impaired Respiration At the usual adult dose of 10 mg/70 kg, NUBAIN (nalbuphine hydrochloride) causes some respiratory depression approximately equal to that produced by equal doses of morphine.”

The firm revised the subsection entitled **Impaired Renal or Hepatic Function** to the following.

“Impaired Renal or Hepatic Function Because NUBAIN is metabolized in the liver and excreted by the kidneys, NUBAIN should be used with caution in patients with renal or liver dysfunction and administered in reduce amounts.”

The firm removed “pre-operative period” from the following sentence.

“Cardiovascular System During evaluation of NUBAIN in anesthesia, a higher incidence of bradycardia has been reported in patients who did not receive atropine pre-operatively ~~or in the pre-operative period.~~”

The firm added the following sub-sections at the end of the **PRECAUTIONS** section.

“Information for Patients

Patients should be advised of the following information:

- NUBAIN is associated with sedation and may impair mental and physical activities required for the performance of potentially dangerous tasks such as driving a car or operating machinery.
- NUBAIN is to be used as prescribed by a physician. Dose or frequency should not be increased without first consulting with a physician since NUBAIN may cause psychological or physical dependence.
- The use of NUBAIN with other ~~drugs~~ can cause signs and symptoms of withdrawal.
- Abrupt discontinuation of NUBAIN after prolonged usage may cause signs and symptoms of withdrawal.

Laboratory Tests

NUBAIN (nalbuphine hydrochloride) may interfere with enzymatic methods for the detection of opioids depending on the specificity/sensitivity of the test. Please consult the test manufacturer for specific details.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was found in a 24-month carcinogenicity study in rats and an 18-month carcinogenicity study in mice at oral doses as high as the equivalent of approximately three times the maximum recommended therapeutic dose.

No evidence of a mutagenic/genotoxic potential to NUBAIN was found in the Ames, Chinese Hamster Ovary HGPRT, and Sister Chromatid Exchange, mouse micronucleus, and rat bone marrow cytogenicity assays. Nalbuphine induced an increased frequency of mutation in mouse lymphoma cells.*

The Agency proposes to replace the section entitled Carcinogenesis, Mutagenesis, Impairment of Fertility to the following.

“Carcinogenesis

Long term carcinogenicity studies were performed in rats (24 months) and mice (19 months) by oral administration at doses up to 200 mg/kg (1180 mg/m²) and 200 mg/kg (600 mg/m²) per day, respectively. There was no evidence of an increase in tumors in either species related to NUBAIN administration. The maximum recommended human dose (MRHD) in a day is 160 mg subcutaneously, intramuscularly or intravenously, or approximately 100 mg/m²/day for a 60 kg subject.

Mutagenesis

NUBAIN did not have mutagenic activity in the AMES test with four bacterial strains, in the Chinese Hamster Ovary HGPRT assays or in the Sister Chromatids Exchange Assay. However, NUBAIN induced an increased frequency of mutation in the mouse lymphoma assay. Clastogenic activity was not observed in the mouse micronucleus test of the cytogenicity bone marrow assay in rats.

Impairment of Fertility

A reproduction study was performed in male and female rats at subcutaneous doses up to 56 mg/kg/day or 330 mg/m²/day. NUBAIN did not affect either male or female fertility rates.”

The firm added the following sub-sections at the end of the PRECAUTIONS section.

Usage in Pregnancy

Teratogenic Effects

~~Pregnancy Category B—Reproduction studies have been performed in rats and in rabbits at dosages as high as approximately 14 and 31 times respectively the maximum recommended daily dose and revealed no evidence of impaired fertility or harm to the fetus due to NUBAIN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed (see WARNINGS).~~

Non-teratogenic Effects

~~Neonatal body weight and survival was reduced when NUBAIN was subcutaneously administered to female rats prior to mating and throughout gestation and lactation or to pregnant rats during the last third of gestation and throughout lactation at doses approximately 8 to 17 times the maximum recommended therapeutic dose. The clinical significance of this effect is unknown.”~~

The Agency proposes to replace the above two sections to the following.

“Teratogenic Effects – Pregnancy Category B

Reproduction studies have been performed in rats by subcutaneous administration of nalbuphine up to 100 mg/kg/day, or 590 mg/m²/day which is approximately 6 times the MRHD, and in rabbits by intravenous administration of nalbuphine up to 32 mg/kg/day, or 378 mg/m²/day which is approximately 4 times the MRHD. The results did not reveal evidence of developmental toxicity, including teratogenicity, 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, this drug should be used during pregnancy only if clearly needed.

Non-Teratogenic Effects

Neonatal body weight and survival rates were reduced at birth and during lactation when nalbuphine was subcutaneously administered to female and male rats prior to mating and throughout gestation and lactation or to pregnant rats during the last third of gestation and throughout lactation at doses approximately 4 times the maximum recommended human dose.”

Use During Labor and Delivery

See WARNINGS.

Nursing Mothers

Limited data suggest that NUBAIN is excreted in maternal milk but only in a small amount (less than 1% of the administered dose) and with a clinically insignificant effect. Caution should be exercised with NUBAIN is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.”

ADVERSE REACTIONS:

The firm modified the third sentence in this section to the following.

“Other adverse reactions which ~~may occur~~ occurred (reported incidence of 1% or less) ~~are~~ were:”

The firm removed “pulmonary edema” from the **Cardiovascular** subsection.

The firm added the following paragraphs at the end of this section.

“**Allergic Reactions** Anaphylactic/anaphylactoid and other serious hypersensitivity reactions have been reported following the use of nalbuphine and may require immediate, supportive medical treatment. These reactions may include shock, respiratory distress, respiratory arrest, bradycardia, cardiac arrest, hypotension, or laryngeal edema. Other allergic-type reactions reported include stridor, bronchospasm, wheezing, edema, rash pruritus, nausea, vomiting, diaphoresis, weakness, and shakiness.

Post-marketing Other reports include pulmonary edema, agitation and injection site reactions such as pain, swelling, redness, burning, and hot sensations.”

DRUG ABUSE AND DEPENDENCE: The firm placed the language from the **WARNINGS Drug Dependence** section to this section.



The Agency proposes to replace the above section to the following.

“There have been reports of abuse and dependence associated with Nubain among health care providers, patients and bodybuilders. There have been reported instances of psychological and physical dependence and tolerance in patients abusing NUBAIN. Individuals with a prior history of opioid or other substance abuse or dependence may be at greater risk in responding to reinforcing properties of NUBAIN.

Abrupt discontinuation of NUBAIN following prolonged use has been followed by symptoms of narcotic withdrawal, i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and piloerection.”

OVERDOSAGE: The following subsection was removed from **DOSAGE AND ADMINISTRATION Management of Overdosage** and placed in this section.

“The immediate intravenous administration of **NARCAN® (naloxone hydrochloride)** an opiate antagonist such as naloxone or nalmefene is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

The administration of single doses of 72 mg of NUBAIN subcutaneously to eight normal subjects has been reported to have resulted primarily in symptoms of sleepiness and mild dysphoria.”

DOSAGE AND ADMINISTRATION: The firm removed the following sub-section and moved it to the **OVERDOSAGE** section.

~~“**Management of Overdosage**—The immediate intravenous administration of NARCAN® (naloxone hydrochloride) is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.~~

~~The administration of single doses of 72 mg of NUBAIN subcutaneously to eight normal subjects has been reported to have resulted primarily in symptoms of sleepiness and mild dysphoria.”~~

The firm added the following sentence before the subsection entitled **Patients Dependent on Narcotics**.

“NUBAIN is physically incompatible with nafcillin and keterolac.”

HOW SUPPLIED: The firm modified this section as follows.

“NUBAIN (nalbuphine hydrochloride) injection for intramuscular, subcutaneous, or intravenous use is a sterile solution available in:

NDC 0590-0508-01 (sulfite-free) 10 mL multiple dose vials (box of 1)

NDC 0590-0432-10 (sulfite/paraben-free) 10 mg/mL, 1 mL ampuls (box of 10)

NDC 0590-0509-01 (sulfite-free) 20 mg/mL, 10 mL multiple dose vials (box of 1)

NDC 0590-0433-10 (sulfite/paraben-free) 20 mg/mL, 1 mL ampuls (box of 10)

Store at controlled room temperature (59 – 86F, 15 –30C). Protect from excessive light. Store in carton until contents have been used.

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

The firm discontinued the 20 mg/mL, 1 mL disposable pre-filled syringes and also noted the deletion in SLR-034.

~~“NDC 0590-0396-15 20 mg/mL, 1 mL disposable pre-filled syringes (box of 10)”~~

SLR-036 may be approved following the implementation of the recommendations outlined below.

1. Per the OPDRA review consult by Janos Bacsanyi, M.D., dated, February 14, 2000, the firm should add **seizures** as one of the adverse drug reactions under the section entitled **ADVERSE REACTIONS Post-marketing**.
2. In the section entitled **CLINICAL PHARMACOLOGY**, the 4th paragraph should be modified as follows.

“NUBAIN may produce the same degree of respiratory depression as equianalgesic doses of morphine. However, NUBAIN exhibits a ceiling effect such that increases in dose greater than 30 mg do not produce further respiratory depression **in the absence of other CNS active medications affecting respiration.**”

3. The section entitled **WARNINGS Use in Pregnancy (other than labor)** should be modified as follows.

“Use in Pregnancy (other than labor) Severe fetal bradycardia has been reported when NUBAIN is administered during labor. Naloxone may reverse these effects. Although there are no reports of fetal bradycardia earlier in pregnancy, it is possible that this may occur. This drug should be used in pregnancy only if clearly needed, if the potential benefit outweighs the risk to the fetus, and if appropriate measures such as fetal monitoring are taken to detect and manage any potential adverse effect on the fetus.”

4. The section entitled **WARNINGS Use During Labor and Delivery** should be modified as follows.

“Use During Labor and Delivery The placental transfer of nalbuphine is ~~high~~ rapid, and variable with a maternal to fetal ratio ranging from 1:0.37 to — tal and neonatal adverse effects that have been reported following the administration of nalbuphine to the mother during labor include fetal bradycardia, respiratory depression at birth, apnea, cyanosis and hypotonia. Maternal administration of naloxone during labor has normalized these effects in some cases. Severe and prolonged fetal bradycardia has been reported. Permanent neurological damage attributed to fetal bradycardia has occurred. A sinusoidal fetal-heart rate pattern associated with the use of nalbuphine has also been reported. NUBAIN should be used during labor and delivery only if clearly indicated and only if the potential benefit outweighs the risk to the infant. ~~with caution in women during labor and delivery, and newborns should be monitored for respiratory depression, apnea, bradycardia and arrhythmias if NUBAIN has been used.”~~

5. In the section entitled **PRECAUTIONS Information for Patients** the following sentences should be revised as follows:

“Abrupt discontinuation of NUBAIN after prolonged usage may cause signs and symptoms of withdrawal.”

Laboratory Tests

NUBAIN (nalbuphine hydrochloride) may interfere with enzymatic methods for the detection of opioids depending on the specificity/sensitivity of the test. Please consult the test manufacturer for specific details.”

6. The section entitled **PRECAUTIONS Carcinogenesis, Mutagenesis, Impairment of Fertility** should be replaced with the following.

Carcinogenesis

Long term carcinogenicity studies were performed in rats (24 months) and mice (19 months) by oral administration at doses up to 200 mg/kg (1180 mg/m²) and 200 mg/kg (600 mg/m²) per day, respectively. There was no evidence of an increase in tumors in either species related to NUBAIN administration. The maximum recommended human dose (MRHD) in a day is 160 mg subcutaneously, intramuscularly or intravenously, or approximately 100 mg/m²/day for a 60 kg subject.

Mutagenesis

NUBAIN did not have mutagenic activity in the AMES test with four bacterial strains, in the Chinese Hamster Ovary HGPRT assays or in the Sister Chromatids Exchange Assay. However, NUBAIN induced an increased frequency of mutation in the mouse lymphoma assay. Clastogenic activity was not observed in the mouse micronucleus test of the cytogenicity bone marrow assay in rats.

Impairment of Fertility

Reproduction study was performed in male and female rats at subcutaneous doses up to 56 mg/kg/day or 330 mg/m²/day. NUBAIN did not affect either male or female fertility rates.”

7. The following sections in **PRECAUTIONS** should be replaced with the following language.

“Teratogenic Effects – Pregnancy Category B

A reproduction studies have been performed in rats by subcutaneous administration of nalbuphine up to 100 mg/kg/day, or 590 mg/m²/day which is approximately 6 times the MRHD, and in rabbits by intravenous

administration of nalbuphine up to 32 mg/kg/day, or 378 mg/m²/day which is approximately 4 times the MRHD. The results did not reveal evidence of developmental toxicity, including teratogenicity, 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, this drug should be used during pregnancy only if clearly needed.

Non-Teratogenic Effects

Neonatal body weight and survival rates were reduced at birth and during lactation when nalbuphine was subcutaneously administered to female and male rats prior to mating and throughout gestation and lactation or to pregnant rats during the last third of gestation and throughout lactation at doses approximately 4 times the maximum recommended human dose.”

8. The section entitled **OVERDOSAGE** should be modified as follows.

“The immediate intravenous administration of NARCAN® (~~naloxone hydrochloride~~) an opiate antagonist such as naloxone or nalmefene is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

9. Replace the DRUG ABUSE and DEPENDENCE section with the following:

There have been reports of abuse and dependence associated with Nubain among health care providers, patients and bodybuilders. There have been reported instances of psychological and physical dependence and tolerance in patients abusing NUBAIN. Individuals with a prior history of opioid or other substance abuse or dependence may be at greater risk in responding to reinforcing properties of NUBAIN.

Abrupt discontinuation of NUBAIN following prolonged use has been followed by symptoms of narcotic withdrawal, i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and piloerection.”

Regulatory Project Manager

Cathie Schumaker/11-23-01
Supervisory Comment/Concurrence

Concurrence by Cynthia G. McCormick/with minor changes incorporated into the text
10-28-01

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/s/

Cathie Schumaker
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CSO