CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74471

Trade Name Nalbuphine Hydrochloride Injection 10mg/ml and 20mg/ml

Generic Name Nalbuphine Hydrochloride Injection 10mg/ml and 20mg/ml

Sponsor King Pharmaceuticals, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74471

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	Included	Pending Completion	Not Prepared	Not Required
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EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74471

APPROVAL LETTER

ANDA 74-471

MAR 19 1998

King Pharmaceuticals, Inc.
Attention: Thomas K. Rogers, III
501 Fifth Street
Bristol, TN 37620

Dear Sir:

This is in reference to your abbreviated new drug application dated February 23, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Nalbuphine Hydrochloride Injection, 10 mg/mL and 20 mg/mL.

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

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Nalbuphine Hydrochloride Injection, 10 mg/mL and 20 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Nubain® Injection, 10 mg/mL and 20 mg/mL, respectively, of DuPont Merck Pharmaceutical Company).

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

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

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

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

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

3-19-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74471

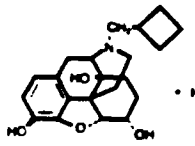
FINAL PRINTED LABELING

NALBUPHINE HYDROCHLORIDE INJECTION

II

DESCRIPTION

Nalbuphine hydrochloride is a synthetic narcotic agonist-antagonist analgesic of the phenanthrene series. It is chemically related to both the widely used narcotic antagonist, naloxone, and the potent narcotic analgesic, oxymorphone.



NALBUPHINE HYDROCHLORIDE
(-) - 17 (cyclobutylmethyl) - 4, 5α - epoxy morphinan- 3, 6 α, 14-triol, hydrochloride

• HCl

$C_{21}H_{27}ClNO_4$ M.W. 393.92

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

CLINICAL PHARMACOLOGY

Nalbuphine hydrochloride is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis.

Its onset of action 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 nalbuphine is one-fourth as potent as nalorphine and 10 times that of pentazocine.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Nalbuphine hydrochloride injection should not be administered to patients who are hypersensitive to it.

WARNINGS

Nalbuphine hydrochloride injection 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 Dependence Nalbuphine has been shown to have a low abuse potential. When compared with drugs which are not mixed agonist-antagonists, it has been reported that nalbuphine's potential for abuse would be less than that of codeine and propoxyphene. Psychological and physical dependence and tolerance may follow the abuse or misuse of nalbuphine. Therefore, caution should be observed in prescribing it for emotionally unstable patients, or for individuals with a history of narcotic abuse. Such patients should be closely supervised when long-term therapy is contemplated.

Care should be taken to avoid increases in dosage or frequency of administration which in susceptible individuals might result in physical dependence.

Abrupt discontinuation of nalbuphine hydrochloride 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.

Use in Ambulatory Patients Nalbuphine may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Therefore, nalbuphine hydrochloride injection 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 nalbuphine hydrochloride effects that would affect driving or other potentially dangerous tasks.

Use in Children Clinical experience to support administration to patients under 18 years is not available at present.

Use in Pregnancy (other than labor) Safe use of nalbuphine hydrochloride 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 the physician, the potential benefits outweigh the possible hazards.

Use During Labor and Delivery Nalbuphine 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 nalbuphine 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 CO_2 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, nalbuphine hydrochloride injection 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 nalbuphine possesses narcotic antagonist activity, there is evidence that in nondependent patients it will not antagonize a narcotic analgesic administered just before, concurrently or just after an injection of nalbuphine hydrochloride. Therefore, patients receiving a narcotic analgesic, general anesthetics, phenothiazines, or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with nalbuphine hydrochloride injection may exhibit an additive effect. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Sulfites Sensitivity Nalbuphine hydrochloride injection contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

Impaired Respiration At the usual adult dose of 10 mg/70 kg, nalbuphine hydrochloride 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 nalbuphine hydrochloride. Respiratory depression induced by nalbuphine hydrochloride can be reversed by naloxone hydrochloride injection when indicated. Nalbuphine hydrochloride injection 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 nalbuphine is metabolized in the liver and excreted by the kidneys, patients with renal or liver dysfunction may overreact to customary doses. Therefore, in these individuals, nalbuphine hydrochloride injection should be used with caution and administered in reduced amounts.

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

Biliary Tract Surgery As with all narcotic analgesics, nalbuphine hydrochloride 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 elevation of nalbuphine hydrochloride injection 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.

ADVERSE REACTIONS

The most frequent adverse reaction in 1086 patients treated with nalbuphine hydrochloride injection is sedation 381 (36%).

Less frequent reactions are sweating/clammy 99 (9%), nausea/vomiting 66 (6%), dizziness/vertigo 58 (5%), dry mouth 44 (4%), and headache 27 (3%).

Other adverse reactions which may occur (reported incidence of 1% or less) are:

CNS Effects Nervousness, depression, restlessness, crying, euphoria, floating, hostility, unusual dreams, confusion, tenseness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality. The incidence of psychotomimetic 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, pulmonary edema.
Gastrointestinal Cramps, dyspepsia, bitter taste.
Respiration Depression, dyspnea, asthma.
Dermatological Itching, burning, urticaria.
Miscellaneous Speech difficulty, urinary urgency, blurred vision, flushing and warmth.

OVERDOSAGE

Management of Overdosage The immediate intravenous administration of naloxone hydrochloride injection 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 nalbuphine hydrochloride injection 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 160 mg.

The use of nalbuphine hydrochloride injection as a supplement to balanced anesthesia requires larger doses than those recommended for analgesia. Induction doses of nalbuphine hydrochloride injection range from 0.3 mg/kg to 3.0 mg/kg intravenously to be administered over a 10 to 15 minute period with maintenance doses of 0.25 to 0.50 mg/kg in single intravenous administrations as required. The use of nalbuphine hydrochloride injection may be followed by respiratory depression which can be reversed with the narcotic antagonist naloxone hydrochloride injection.

Patients Dependent on Narcotics Patients who have been taking narcotics chronically may experience withdrawal symptoms upon the administration of nalbuphine hydrochloride injection. If unduly troublesome, narcotic 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 narcotic with similar duration of activity, one-fourth of the anticipated dose of nalbuphine hydrochloride injection 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 used at appropriate intervals until the desired level of analgesia is obtained with nalbuphine hydrochloride injection.

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

HOW SUPPLIED

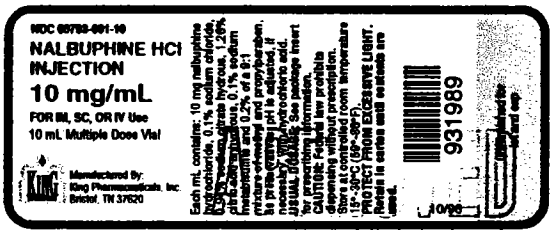
Nalbuphine hydrochloride injection for intramuscular, subcutaneous, or intravenous use is available in:

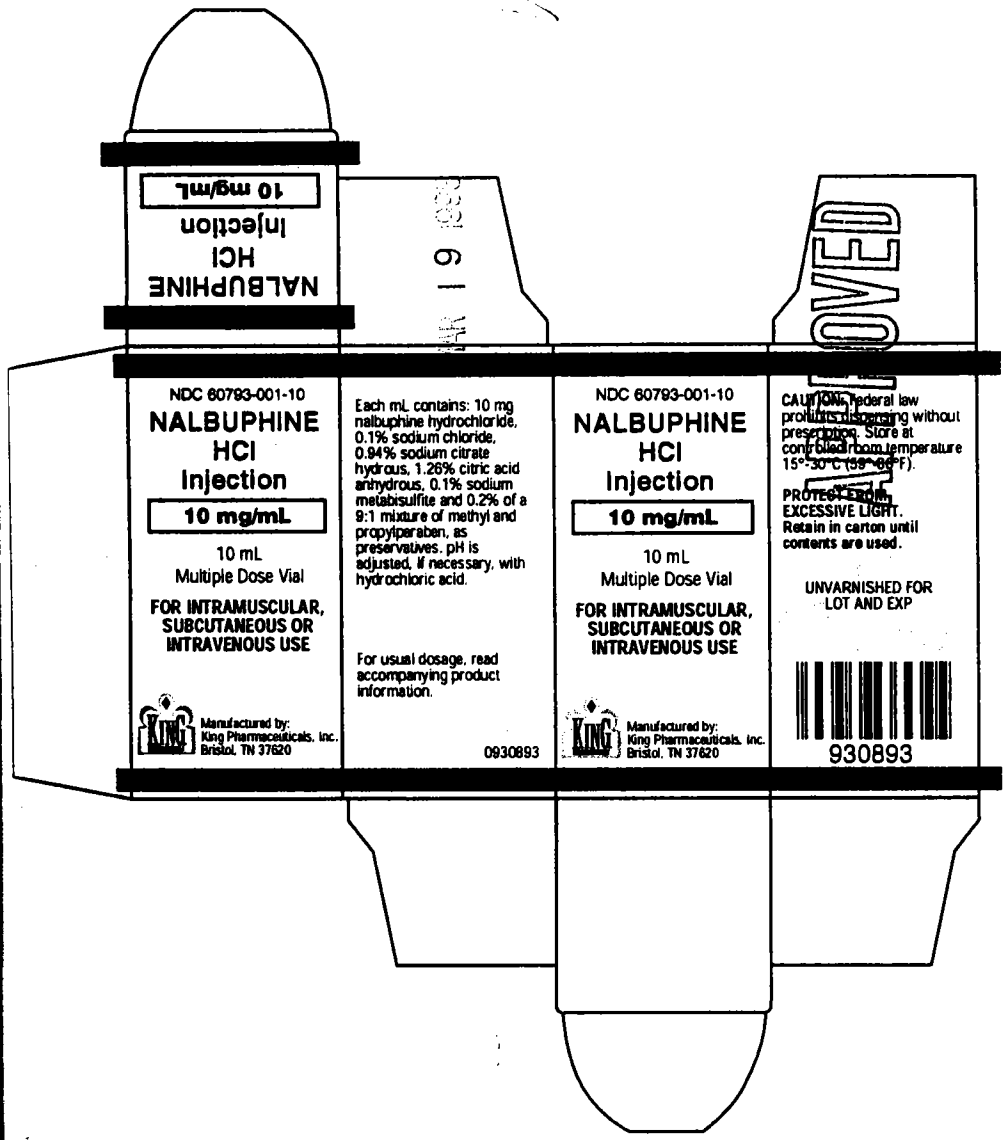
NDC 60793-091-10	10 mg/mL, 10 mL multiple dose vials (box of 1)
NDC 60793-092-10	20 mg/mL, 10 mL multiple dose vials (box of 1)

Store at controlled room temperature 15°-30°C (59°-86°F).
PROTECT FROM EXCESSIVE LIGHT.
Retain in carton until contents are used.

Manufactured by
King Pharmaceuticals, Inc
Bristol, TN 37620

0931988
Revised 6/95


NDC 66758-691-10
NALBUPHINE HCl
INJECTION
10 mg/mL
FOR IM, SC, OR IV Use
10 mL Multiple Dose Vial
Manufactured By:
Ring Pharmaceuticals, Inc.
Bristol, TN 37620
931989


NALBUPHINE HCl Injection
10 mg/mL
NDC 60793-001-10
NALBUPHINE HCl Injection
10 mg/mL
10 mL
Multiple Dose Vial
FOR INTRAMUSCULAR, SUBCUTANEOUS OR INTRAVENOUS USE
Manufactured by:
King Pharmaceuticals, Inc.
Bristol, TN 37620
Each mL contains: 10 mg nalbuphine hydrochloride, 0.1% sodium chloride, 0.94% sodium citrate hydrous, 1.26% citric acid anhydrous, 0.1% sodium metabisulfite and 0.2% of a 9:1 mixture of methyl and propylparaben, as preservatives. pH is adjusted, if necessary, with hydrochloric acid.
For usual dosage, read accompanying product information.
0930893
CAUTION: Federal law prohibits dispensing without prescription. Store at controlled room temperature 15°-30°C (59°-86°F).
PROTECT FROM EXCESSIVE LIGHT. Retain in carton until contents are used.
UNVARNISHED FOR LOT AND EXP
930893


NALBUPHINE HCl Injection
10 mg/mL
NDC 60793-001-10
NALBUPHINE HCl Injection
10 mg/mL
10 mL
Multiple Dose Vial
FOR INTRAMUSCULAR, SUBCUTANEOUS OR INTRAVENOUS USE
Manufactured by:
King Pharmaceuticals, Inc.
Bristol, TN 37620
Each mL contains: 10 mg nalbuphine hydrochloride, 0.1% sodium chloride, 0.94% sodium citrate hydrous, 1.26% citric acid anhydrous, 0.1% sodium metabisulfite and 0.2% of a 9:1 mixture of methyl and propylparaben, as preservatives. pH is adjusted, if necessary, with hydrochloric acid.
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UNVARNISHED FOR LOT AND EXP
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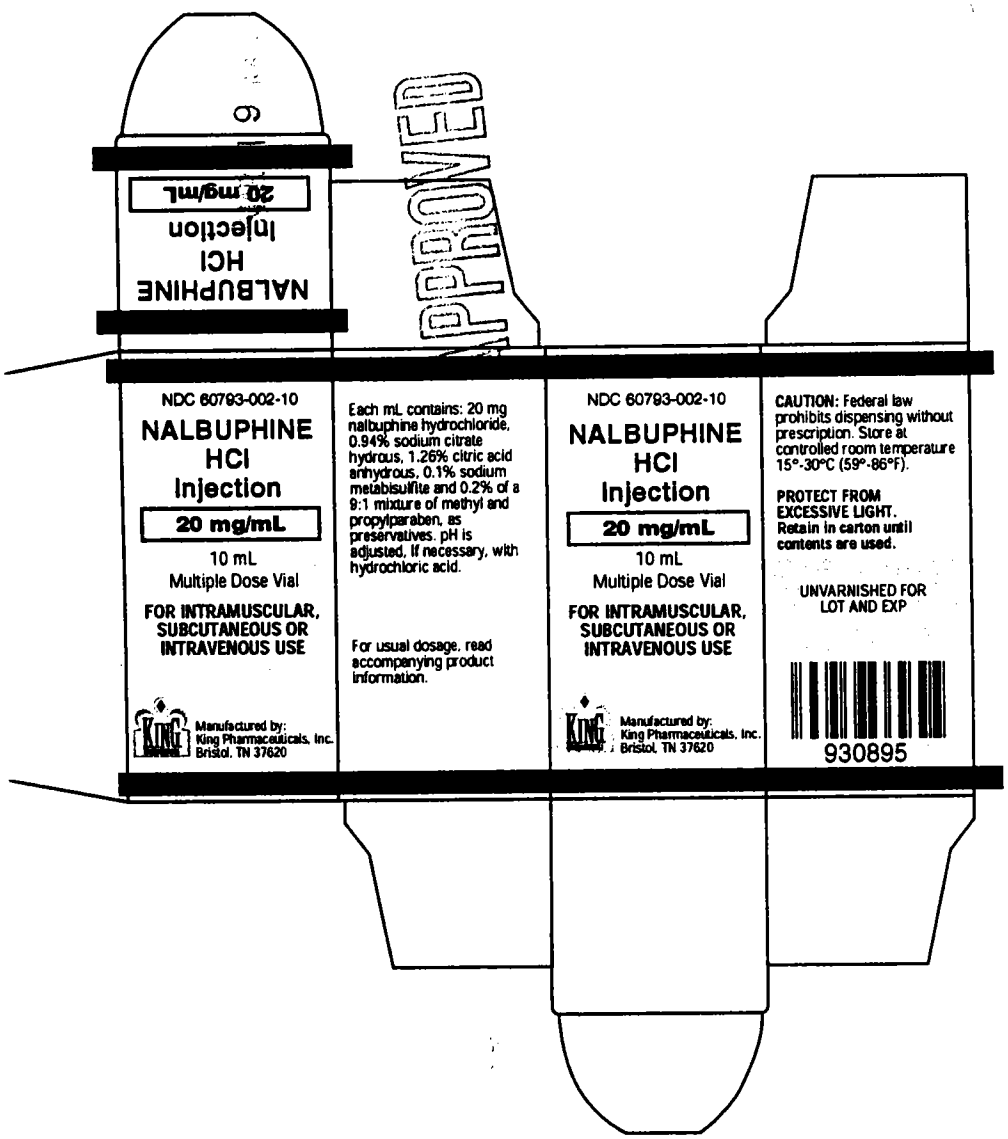
APPROVED
NALBUPHINE HCl Injection
20 mg/mL
NDC 60793-002-10
NALBUPHINE HCl Injection
20 mg/mL
10 mL
Multiple Dose Vial
FOR INTRAMUSCULAR, SUBCUTANEOUS OR INTRAVENOUS USE
Manufactured by: King Pharmaceuticals, Inc. Bristol, TN 37620
Each mL contains: 20 mg nalbuphine hydrochloride, 0.94% sodium citrate hydrous, 1.26% citric acid anhydrous, 0.1% sodium metabisulfite and 0.2% of a 9:1 mixture of methyl and propylparaben, as preservatives. pH is adjusted, if necessary, with hydrochloric acid.
For usual dosage, read accompanying product information.
NDC 60793-002-10
NALBUPHINE HCl Injection
20 mg/mL
10 mL
Multiple Dose Vial
FOR INTRAMUSCULAR, SUBCUTANEOUS OR INTRAVENOUS USE
Manufactured by: King Pharmaceuticals, Inc. Bristol, TN 37620
CAUTION: Federal law prohibits dispensing without prescription. Store at controlled room temperature 15°-30°C (59°-86°F).
PROTECT FROM EXCESSIVE LIGHT. Retain in carton until contents are used.
UNVARNISHED FOR LOT AND EXP
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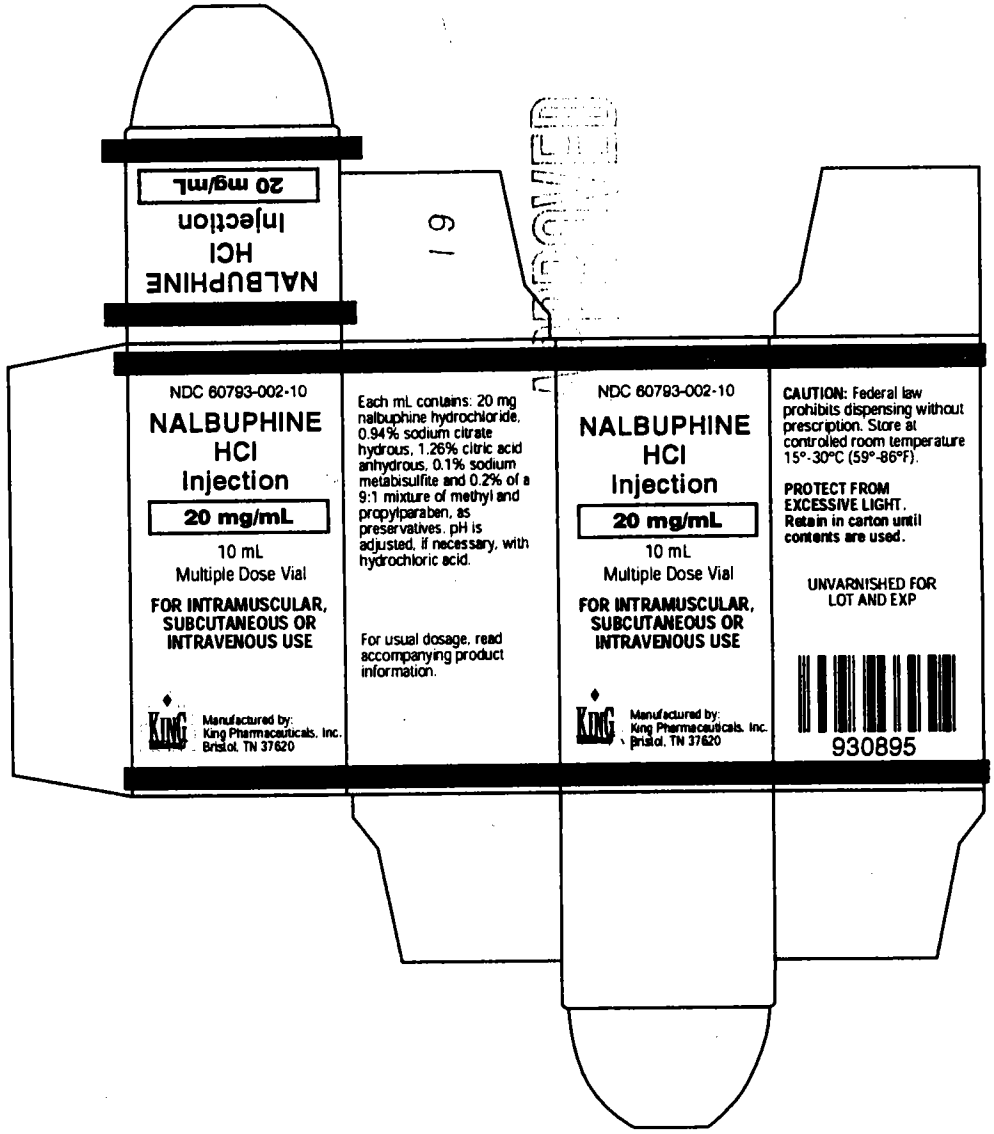
APPROVED
NALBUPHINE HCl Injection
20 mg/mL
NDC 60793-002-10
NALBUPHINE HCl Injection
20 mg/mL
10 mL
Multiple Dose Vial
FOR INTRAMUSCULAR, SUBCUTANEOUS OR INTRAVENOUS USE
Manufactured by: King Pharmaceuticals, Inc. Bristol, TN 37620
Each mL contains: 20 mg nalbuphine hydrochloride, 0.94% sodium citrate hydrous, 1.26% citric acid anhydrous, 0.1% sodium metabisulfite and 0.2% of a 9:1 mixture of methyl and propylparaben, as preservatives. pH is adjusted, if necessary, with hydrochloric acid.
For usual dosage, read accompanying product information.
NDC 60793-002-10
NALBUPHINE HCl Injection
20 mg/mL
10 mL
Multiple Dose Vial
FOR INTRAMUSCULAR, SUBCUTANEOUS OR INTRAVENOUS USE
Manufactured by: King Pharmaceuticals, Inc. Bristol, TN 37620
CAUTION: Federal law prohibits dispensing without prescription. Store at controlled room temperature 15°-30°C (59°-86°F).
PROTECT FROM EXCESSIVE LIGHT. Retain in carton until contents are used.
UNVARNISHED FOR LOT AND EXP
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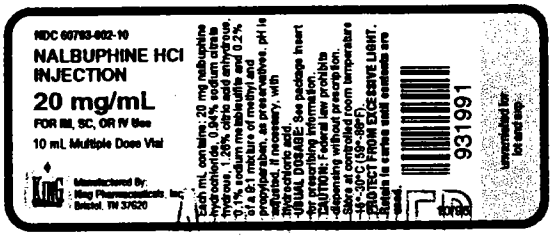

NDC 60793-602-10
NALBUPHINE HCl
INJECTION
20 mg/mL
FOR IM, SC, OR IV Use
10 mL Multiple Dose Vial
Manufactured By:
Meg Pharmaceuticals, Inc.
Bristol, TN 37620
Each mL contains: 20 mg nalbuphine hydrochloride, 0.94% sodium citrate dihydrous, 1.26% citric acid anhydrous, 0.1% sodium metabisulfite and 0.2% of a 9:1 mixture of methyl and propylparaben, as preservatives. pH is adjusted, if necessary, with hydrochloric acid.
USUAL DOSAGE: See package insert for prescribing information.
CAUTION: Federal law prohibits dispensing without prescription.
Store at controlled room temperature 15°-30°C (59°-86°F).
PROTECT FROM EXCESSIVE LIGHT.
Return to carton until contents are used.
931991
unscrambled for
lot and exp

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74471

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 74-471

3. NAME AND ADDRESS OF APPLICANT
King Pharmaceuticals, Inc.
Attention: Thomas K. Rogers
501 Fifth Street
Bristol, TN 37602

4. BASIS OF SUBMISSION
Nubain® (Nalbuphine Hydrochloride) Injection;
DuPont Pharmaceuticals

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Nalbuphine HCl Injection

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

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: February 23, 1994
New Corresp. (Meeting request): April 11, 1994
New Corresp. (Meeting request): April 29, 1994
New Corresp. (Scale-up): August 5, 1994
Amendment: August 8, 1994
New Corresp. (Methods): November 11, 1994
New Corresp.: September 14, 1995
Amendment (Chemistry & Labeling): February 1, 1996
Amendment (Chemistry & Labeling): December 3, 1996
Amendment: (Chemistry/Micro/Label): May 29, 1997
(Bolded item subject of this review)

FDA:
Refusal to File Letter: March 24, 1994
Acknowledgement: September 2, 1994
Letter; C.R. # 1: March 1, 1995
Letter; C.R. # 2: August 30, 1996
Letter; C.R. # #: February 14, 1997

10. PHARMACOLOGICAL CATEGORY
Analgesic (Synthetic narcotic)

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

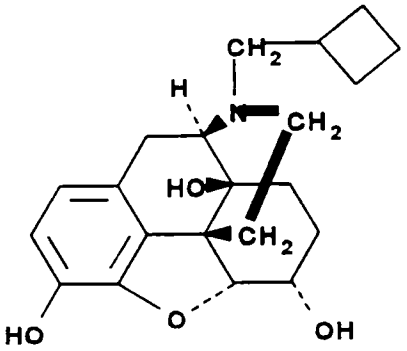
13. DOSAGE FORM
Injection
(10 mL multiple dose vial)

14. POTENCIES
10 mg/mL & 20 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Nalbuphine Hydrochloride

$C_{21}H_{27}NO_4.HCl$; M.W. = 393.91



• HCl

17-(Cyclobutylmethyl)-4,5α-epoxymorphinan-3,6α,14-triol hydrochloride. CAS [23277-43-2]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

a. CMC issues are satisfactory.
b. Label review is satisfactory for approval 11/21/97.
c. Microbiological review is satisfactory 10/28/97.
d. EIRs for King Pharmaceutical and are pending - EES 10/28/97. .
e. Bio satisfactory, waiver granted 11/29/94.
f. Methods validation satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

This application can be approved upon satisfactory EIR for

19. REVIEWER: Donald Shostak

DATE COMPLETED: October 28, 1997
(Revised 11/24/97 - labeling)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74471

BIOEQUIVALENCE REVIEW(S)

NOV 2 9 1994

Nalbuphine Hydrochloride Injection
10 mg/mL and 20 mg/mL,
10 mL Multidose Vial
ANDA #74-471
Reviewer: Moo Park
Filename: 74471W.294

King Pharmaceuticals
Bristol, TN
Submission Date:
February 23, 1994

Review of a Waiver Request

I. Objective

Review of King Pharmaceuticals's waiver request on its test product Nalbuphine Hydrochloride Injection, 10 mL multidose vials of 10 mg/mL and 20 mg/mL strengths. The reference product is Du Pont Pharmaceuticals's Nubain^{R} Injection, 10 mL multidose vials of 10 mg/mL and 20 mg/mL strengths.

II. Comments

1. Formulations of the test and reference products are compared in Table 1 as described in Section VII of the ANDA. The test and reference formulations are qualitatively and quantitatively identical. The firm used 5% overage for parabens.

   The firm did not list the formulations without sulfite and parabens, even though these formulations were mentioned in the package insert.

Table 1. Comparison of Formulations
Unit: %W/V

Ingredient	10 mg/mL		20 mg/mL	
	Test	Ref	Test	Ref
Nalbuphine HCl	1.0	1.0	2.0	2.0
Sodium Citrate, Hydrous				
Citric Acid, Anhydrous				
Sodium Meta-bisulfite				
Sodium Chloride				
Methylparaben				
Propylparaben				
HCl Solution				
Sodium Hydroxide Solution				
Water for Injectio				

2. Waiver of bioequivalence study requirements is granted for the formulations with sulfite and parabens as shown in Table 1.

3. The firm should submit a waiver request for the formulations without sulfite and parabens.

III. Deficiency

The firm should submit a separate waiver request for the formulations without sulfite and parabens.

IV. Recommendations

1. The Division of Bioequivalence agrees that the information submitted by King Pharmaceuticals demonstrate that Nalbuphine Hydrochloride Injection with sulfite and parabens, 10 mL multidose vials of 10 mg/mL and 20 mg/mL strengths, falls under 21 CFR Section 320.22 (b) of the Bioavailability/ Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the 10 mL multidose vials with sulfite and parabens of 10 mg/mL and 20 mg/mL strengths of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulations with sulfite and parabens, 10 mL multidose vials of 10 mg/mL and 20 mg/mL strengths to be

bioequivalent to Du Pont's Nubain[R] Injection with sulfite and parabens, 10 mL multidose vials of 10 mg/mL and 20 mg/mL strengths.

2. This waiver is granted only for the formulations containing the sulfite and parabens.

The firm should be informed of the deficiency and recommendations.

Moo Park, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRF 11/29/94

Ramakant M. Mhatre, Ph.D.
Branch Chief, Review Branch III
Division of Bioequivalence

cc: ANDA #74-471 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-658 (Mhatre, Park), Drug File, Division File

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74471

MICROBIOLOGY REVIEW(S)

OFFICE OF GENERIC DRUGS, HFD-640
Microbiologist's Review #2
October 28, 1997

A. 1. **ANDA** 74-471

APPLICANT King Pharmaceuticals, Inc.

2. PRODUCT NAMES: Nalbuphine Hydrochloride Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 10 mg/mL and 20 mg/mL, 10 mL Multiple Dose Vials, Intravenous, Intramuscular, Subcutaneous

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Narcotic Analgesic

B. 1. DATE OF INITIAL SUBMISSION: February 23, 1994
(Received February 24, 1994)

2. DATE OF AMENDMENT: May 29, 1997
Subject of this Review (Received, May 30, 1997)

3. RELATED DOCUMENTS: None
4. ASSIGNED FOR REVIEW: 10/28/97

C. REMARKS: The amendment provides for the response to the microbiology deficiency in the letter dated February 14, 1997.

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes".

10/28/97

Andrea S. High, Ph. D.

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
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