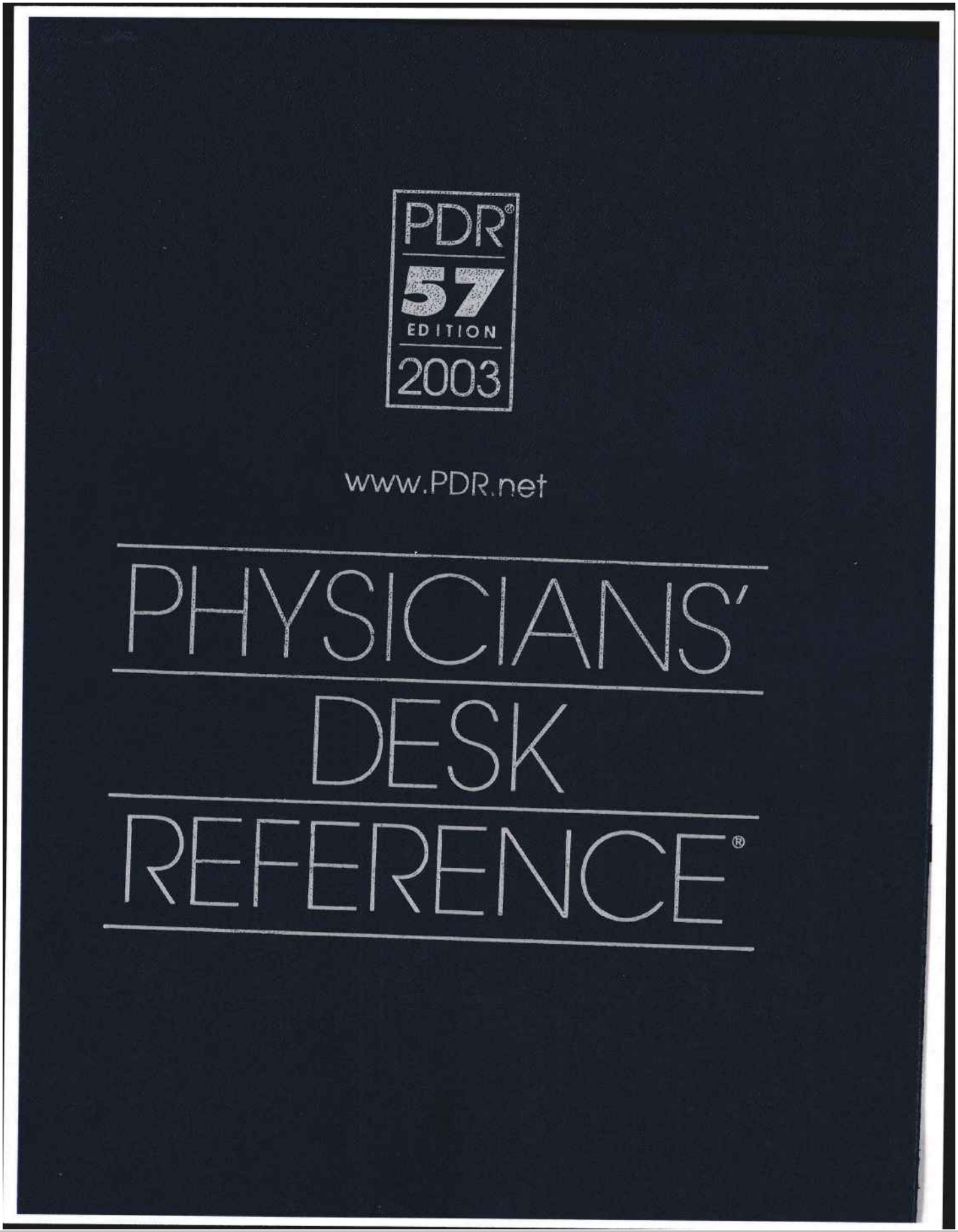

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57 EDITION

2003

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Moban—Cont.

cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Drug Interactions

Potentiation of drugs administered concurrently with MOBAN has not been reported. Additionally, animal studies have not shown increased toxicity when MOBAN is given concurrently with representative members of three classes of drugs (i.e., barbiturates, chloral hydrate and antiparkinson drugs).

ADVERSE REACTIONS

CNS EFFECTS

The most frequently occurring effect is initial drowsiness that generally subsides with continued usage of the drug or lowering of the dose.

Noted less frequently were depression, hyperactivity and euphoria.

Neurological

Extrapyramidal Reactions

Extrapyramidal reactions noted below may occur in susceptible individuals and are usually reversible with appropriate management.

Akathisia

Motor restlessness may occur early.

Parkinson Syndrome

Akinesia, characterized by rigidity, immobility and reduction of voluntary movements and tremor, have been observed. Occurrence is less frequent than akathisia.

Dystonic Syndrome

Prolonged abnormal contractions of muscle groups occur infrequently. These symptoms may be managed by the addition of a synthetic antiparkinson agent (other than L-dopa), small doses of sedative drugs, and/or reduction in dosage.

Tardive Dyskinesia

Antipsychotic drugs are known to cause a syndrome of dyskinetic movements commonly referred to as tardive dyskinesia. The movements may appear during treatment or upon withdrawal of treatment and may be either reversible or irreversible (i.e., persistent) upon cessation of further neuroleptic administration.

The syndrome is known to have a variable latency for development and the duration of the latency cannot be determined reliably. It is thus wise to assume that any antipsychotic agent has the capacity to induce the syndrome and act accordingly until sufficient data has been collected to settle the issue definitively for a specific drug product. In the case of antipsychotic known to produce the irreversible syndrome, the following has been observed.

Tardive dyskinesia has appeared in some patients on long-term therapy and has also appeared after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). There may be involuntary movements of extremities.

There is no known effective treatment of tardive dyskinesia; antiparkinsonism agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked. It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time the syndrome may not develop (See WARNINGS).

Autonomic Nervous System

Occasionally blurring of vision, tachycardia, nausea, dry mouth and salivation have been reported. Urinary retention and constipation may occur particularly if anticholinergic drugs are used to treat extrapyramidal symptoms. One patient being treated with MOBAN (molindone hydrochloride) experienced priapism which required surgical intervention, apparently resulting in residual impairment of erectile function.

Laboratory Tests

There have been rare reports of leucopenia and leucocytosis. If such reactions occur, treatment with MOBAN may continue if clinical symptoms are absent. Alterations of blood glucose, B.U.N., and red blood cells have not been considered clinically significant.

Metabolic and Endocrine Effects

Alteration of thyroid function has not been significant. Amenorrhea has been reported infrequently. Resumption of menses in previously amenorrheic women has been reported. Initially heavy menses may occur. Galactorrhea and gynecomastia have been reported infrequently. Increase in libido has been noted in some patients. Impotence has not been reported. Although both weight gain and weight loss have been in the direction of normal or ideal weight, excessive weight gain has not occurred with MOBAN.

Hepatic Effects

There have been rare reports of clinically significant alterations in liver function in association with MOBAN use.

Cardiovascular

Rare, transient, non-specific T wave changes have been reported on E.K.G. Association with a clinical syndrome has not been established. Rarely has significant hypotension been reported.

Ophthalmological

Lens opacities and pigmentary retinopathy have not been reported where patients have received MOBAN. In some patients, phenothiazine induced lenticular opacities have resolved following discontinuation of the phenothiazine while continuing therapy with MOBAN.

Skin

Early, non-specific skin rash, probably of allergic origin, has occasionally been reported. Skin pigmentation has not been seen with MOBAN usage alone.

MOBAN has certain pharmacological similarities to other antipsychotic agents. Because adverse reactions are often extensions of the pharmacological activity of a drug, all of the known pharmacological effects associated with other antipsychotic drugs should be kept in mind when MOBAN is used. Upon abrupt withdrawal after prolonged high dosage an abstinence syndrome has not been noted.

OVERDOSAGE

Symptomatic, supportive therapy should be the rule.

Gastric lavage is indicated for the reduction of absorption of MOBAN which is freely soluble in water.

Since the adsorption of MOBAN by activated charcoal has not been determined, the use of this antidote must be considered of theoretical value.

Emesis in a comatose patient is contraindicated. Additionally, while the emetic effect of apomorphine is blocked by MOBAN in animals, this blocking effect has not been determined in humans.

A significant increase in the rate of removal of unmetabolized MOBAN from the body by forced diuresis, peritoneal or renal dialysis would not be expected. (Only 2% of a single ingested dose of MOBAN is excreted unmetabolized in the urine). However, poor response of the patient may justify use of these procedures.

While the use of laxatives or enemas might be based on general principles, the amount of unmetabolized MOBAN in feces is less than 1%. Extrapyramidal symptoms have responded to the use of diphenhydramine (Benadryl*), Amantadine HCl (Symmetrel®*) and the synthetic anticholinergic antiparkinson agents, (i.e., Artane*, Cogentin*, Akineton*).

DOSAGE AND ADMINISTRATION

Initial and maintenance doses of MOBAN (molindone hydrochloride) should be individualized.

Initial Dosage Schedule

The usual starting dosage is 50–75 mg/day.

- — Increase to 100 mg/day in 3 or 4 days.
- — Based on severity of symptomatology, dosage may be titrated up or down depending on individual patient response.
- — An increase to 225 mg/day may be required in patients with severe symptomatology.

Elderly and debilitated patients should be started on lower dosage.

Maintenance Dosage Schedule

1. Mild-5 mg-15 mg three or four times a day.
2. Moderate-10 mg-25 mg three or four times a day.
3. Severe-225 mg/day may be required.

HOW SUPPLIED

As tablets in bottles of 100 with potencies and colors as follows:

[See table at top of previous page]

As a concentrate (clear, colorless to straw-yellow syrup) containing 20 mg molindone hydrochloride per mL in 4 oz. (120 mL) bottles, NDC 63481-460-04.

Store at controlled room temperature 15°–30°C (59°–86°F). Protect from light.

*Benadryl-Trademark, Warner-Lambert.
*Symmetrel-Trademark, Endo Pharmaceuticals Inc.
*Artane-Trademark, Lederle Laboratories
*Cogentin-Trademark, Merck & Co., Inc.
*Akineton-Trademark, Knoll Laboratories.

6500-01/December, 2000

Shown in Product Identification Guide, page 312

NARCAN® Rx

[nar'kan]

(Naloxone Hydrochloride Injection, USP)

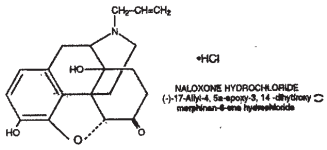
Opioid Antagonist

DESCRIPTION

NARCAN (naloxone hydrochloride injection, USP), an opioid antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.

[See chemical structure at top of next column]

Naloxone hydrochloride occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in



NALOXONE HYDROCHLORIDE
(-)-17-Allyl-4, 5α-epoxy-3, 14 -dihydroxy morphinan-6-one hydrochloride

strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

NARCAN injection is available as a sterile solution for intravenous, intramuscular and subcutaneous administration in three concentrations: 0.02 mg, 0.4 mg and 1 mg of naloxone hydrochloride per mL. pH is adjusted to 3.5 ± 0.5 with hydrochloric acid.

The 0.02 mg/mL strength is a paraben-free formulation containing 9 mg/mL sodium chloride.

The 0.4 mg/mL vial contains 8.6 mg/mL of sodium chloride and 2 mg/mL of methylparaben and propylparaben as preservatives in a ratio of 9:1. The 0.4 mg/mL ampul is available in a paraben-free formulation containing 9 mg/mL of sodium chloride.

The 1 mg/mL vial contains 8.35 mg/mL of sodium chloride and 2 mg/mL of methylparaben and propylparaben as preservatives in a ratio of 9:1. The 1 mg/mL ampul is available in a paraben-free formulation containing 9 mg/mL of sodium chloride.

CLINICAL PHARMACOLOGY

Complete or Partial Reversal of Opioid Depression

NARCAN prevents or reverses the effects of opioids including respiratory depression, sedation and hypotension. Also, it can reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.

NARCAN is an essentially pure opioid antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other opioid antagonists; NARCAN does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity.

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

In the presence of physical dependence on opioids NARCAN will produce withdrawal symptoms.

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

When NARCAN is administered intravenously, the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN. Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN, however, will also be dependent upon the amount, type and route of administration of the opioid being antagonized.

Following parenteral administration, NARCAN is rapidly distributed in the body. It is metabolized in the liver, primarily by glucuronide conjugation and excreted in urine. In one study the serum half-life in adults ranged from 30 to 81 minutes (mean 64 ± 12 minutes). In a neonatal study the mean plasma half-life was observed to be 3.1 ± 0.5 hours.

Adjunctive Use in Septic Shock

Although the mechanism of action is not completely understood, NARCAN appears to block endorphin-mediated hypotension in septic shock patients.

NARCAN has been shown in some cases of septic shock to produce a rise in blood pressure that may last up to several hours; however, this pressor response has not been demonstrated to improve patient survival.

Patients who have responded to NARCAN received the drug early in the course of treatment of septic shock. Because of the limited number of patients who have been treated, optimal dosage and treatment regimens have not been established. Published reports demonstrating a pressor effect have evaluated single bolus injections of 0.4 mg over three (3) to five (5) minutes, which have been repeated for 3–5 doses depending on the response. Bolus infusion doses ranging from 0.03 mg/kg to 0.2 mg/kg over five (5) minutes have also been reported. If a response was elicited, treatment was continued by intravenous infusion of concentrations of 0.03 mg/kg/hour to 0.3 mg/kg/hour for 1–24 hours or more depending upon the clinical response.

INDICATIONS AND USAGE

NARCAN is indicated for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine and butorphanol. NARCAN is also indicated for the diagnosis of suspected opioid tolerance or acute opioid overdosage.

NARCAN may be useful as an adjunctive agent to increase blood pressure in the management of septic shock (see **CLINICAL PHARMACOLOGY; Adjunctive Use in Septic Shock**).

CONTRAINDICATIONS

NARCAN is contraindicated in patients known to be hypersensitive to naloxone hydrochloride or to any of the other ingredients in NARCAN.

WARNINGS

NARCAN should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

The signs and symptoms of opioid withdrawal in a patient physically dependent on opioids may include, but are not limited to, the following: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. In the neonate, opioid withdrawal may also include: convulsions, excessive crying, and hyperactive reflexes.

The patient who has satisfactorily responded to NARCAN should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary, since the duration of action of some opioids may exceed that of NARCAN.

NARCAN is not effective against respiratory depression due to non-opioid drugs. Reversal of buprenorphine-induced respiratory depression may be incomplete. If an incomplete response occurs, respirations should be mechanically assisted.

PRECAUTIONS

General

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

Abrupt postoperative reversal of opioid depression may result in nausea, vomiting, sweating, tremulousness, tachycardia, increased blood pressure, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest which may result in death.

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest have been reported in postoperative patients. Death, coma, and encephalopathy have been reported as sequelae of these events. These have occurred in patients most of whom had pre-existing cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, NARCAN should be used with caution in patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects, such as hypotension, ventricular tachycardia or fibrillation, and pulmonary edema. It has been suggested that the pathogenesis of pulmonary edema associated with the use of NARCAN is similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals to assess the carcinogenic potential of NARCAN have not been conducted. NARCAN was weakly positive in the Ames mutagenicity and *in vitro* human lymphocyte chromosome aberration tests and was negative in the *in vitro* Chinese hamster V79 cell HGPRT mutagenicity assay and in an *in vivo* rat bone marrow chromosome aberration study. Reproduction studies conducted in mice and rats at doses as high as 50 times the usual human dose (10 mg/day) demonstrated no impairment of fertility.

Use in Pregnancy

Teratogenic Effects Pregnancy Category B: Reproduction studies performed in mice and rats at doses as high as 50 times the usual human dose (10 mg/day), revealed no evidence of impaired fertility or harm to the fetus due to NARCAN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, NARCAN should be used during pregnancy only if clearly needed.

Non-teratogenic Effects: Risk-benefit must be considered before NARCAN is administered to a pregnant woman who is known or suspected to be opioid-dependent since maternal dependence may often be accompanied by fetal dependence. Naloxone crosses the placenta and may precipitate withdrawal in the fetus as well as in the mother.

Use in Labor and Delivery

It is not known if NARCAN affects the duration of labor and/or delivery.

Nursing Mothers

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

Usage in Pediatric Patients and Neonates for Septic Shock

The safety and effectiveness of NARCAN in the treatment of hypotension in pediatric patients and neonates with septic shock have not been established.

Renal Insufficiency/Failure

The safety and effectiveness of NARCAN in patients with renal insufficiency/failure have not been established in well-controlled clinical trials. Caution should be exercised when NARCAN is administered to this patient population.

0.4 mg/mL	10 mL multiple dose vial-box of 1	NDC 63481-365-05
0.4 mg/mL (paraben-free)	1 mL ampul-box of 10	NDC 63481-358-10
1 mg/mL	10 mL multiple dose vial-box of 1	NDC 63481-368-05
1 mg/mL (paraben-free)	2 mL ampul-box of 10	NDC 63481-377-10
0.02 mg/mL (paraben-free)	2 mL ampul-box of 10	NDC 63481-359-10

Liver Disease

The safety and effectiveness of NARCAN in patients with liver disease have not been established in well-controlled clinical trials. In one small study in patients with liver cirrhosis, plasma naloxone concentrations were approximately six times higher than in patients without liver disease. NARCAN was well tolerated and no adverse events were reported. Caution should be exercised when NARCAN is administered to patients with liver disease.

ADVERSE REACTIONS

Postoperative

The following adverse events have been associated with the use of NARCAN (naloxone hydrochloride injection, USP) in postoperative patients: hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of NARCAN in postoperative patients may result in significant reversal of analgesia and may cause agitation (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**; **Usage in Adults**; **Postoperative Opioid Depression**).

Opioid Depression

Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest which may result in death (see **PRECAUTIONS**).

Opioid Dependence

Abrupt reversal of opioid effects in persons who are physically dependent on opioids may precipitate an acute withdrawal syndrome which may include, but is not limited to, the following signs and symptoms: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia. In the neonate, opioid withdrawal may also include: convulsions; excessive crying; hyperactive reflexes (see **WARNINGS**).

Agitation and paresthesias have been infrequently reported with the use of NARCAN.

DRUG ABUSE AND DEPENDENCE

NARCAN is an opioid antagonist. Physical dependence associated with the use of NARCAN has not been reported. Tolerance to the opioid antagonist effect of NARCAN is not known to occur.

OVERDOSAGE

There is limited clinical experience with NARCAN overdosage in humans.

Adult Patients

In one study, volunteers and morphine-dependent subjects who received 24 mg/70 kg did not demonstrate toxicity.

In another study, 36 patients with acute stroke received a loading dose of 4 mg/kg (10 mg/m^2/min) of NARCAN followed immediately by 2 mg/kg/hr for 24 hours. There were a few reports of serious adverse events: seizures (2 patients), severe hypertension (1), and hypotension and/or bradycardia (3).

At doses of 2 mg/kg in normal subjects, memory impairment has been reported.

Pediatric Patients

Up to 11 doses of 0.2 mg of naloxone (2.2 mg) have been administered to children following overdose of diphenoxylate hydrochloride with atropine sulfate. Pediatric reports include a 2-1/2 year-old child who inadvertently received a dose of 20 mg of naloxone and a 4-1/2 year-old child who received 11 doses during a 12-hour period, both of whom had no adverse sequelae.

Patient Management

Patients who experience a NARCAN overdose should be treated symptomatically in a closely supervised environment. Physicians should contact a poison control center for the most up-to-date patient management information.

Animal Data

The intravenous single-dose LD_{50} (95% confidence limits) in rats and mice is 150 (135–165) mg/kg and 109 (97–121) mg/kg, respectively. In newborn rats, the subcutaneous single-dose LD_{50} (95% confidence limits) is 260 (228–296) mg/kg. Subcutaneous injection in rats at 100 mg/kg/day for three weeks produced only transiently increased salivation and partial ptosis; no drug-related effects were seen at 10 mg/kg/day for three weeks.

Some chemical impurities in naloxone, i.e., noroxymorphone and bisnaloxone, have been shown to produce emesis in dogs when administered alone at I.V. doses equivalent to impurity levels present in naloxone at 60 times the usual human dose (10 mg/day).

DOSAGE AND ADMINISTRATION

NARCAN may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration, which is recommended in emergency situations.

Since the duration of action of some opioids may exceed that of NARCAN, the patient should be kept under continued surveillance. Repeated doses of NARCAN should be administered, as necessary.

Intravenous Infusion

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

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

General

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

Usage in Adults

Opioid Overdose—Known or Suspected: An initial dose of 0.4 mg to 2 mg of NARCAN may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions are not obtained, it may be repeated at two- to three-minute intervals. If no response is observed after 10 mg of NARCAN have been administered, the diagnosis of opioid-induced or partial opioid-induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

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

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

NARCAN Challenge Test

Used for the diagnosis of suspected opioid tolerance or acute opioid overdosage.

The NARCAN challenge test should not be performed in a patient showing clinical signs or symptoms of opioid withdrawal, or in a patient whose urine contains opioids. The NARCAN challenge test may be administered by either the intravenous or subcutaneous routes.

Intravenous: Inject 0.2 mg NARCAN. Observe for 30 seconds for signs or symptoms of withdrawal. If no evidence of withdrawal, inject 0.6 mg NARCAN. Observe for an additional 20 minutes.

Subcutaneous: Administer 0.8 mg NARCAN. Observe for 20 minutes for signs or symptoms of withdrawal.

Note: Individual patients, especially those with opioid dependence, may respond to lower doses of NARCAN. In some cases, 0.1 mg I.V. NARCAN has produced a diagnostic response.

Interpretation of the Challenge

Monitor vital signs and observe the patient for signs and symptoms of opioid withdrawal. These may include, but are not limited to: nausea, vomiting, dysphoria, yawning, sweating, tearing, rhinorrhea, stuffy nose, craving for opioid, poor appetite, abdominal cramps, sense of fear, skin erythema, disrupted sleep patterns, fidgeting, uneasiness, poor ability to focus, mental lapses, muscle aches or cramps, pupillary dilation, piloerection, fever, changes in blood pressure, pulse or temperature, anxiety, depression, irritability, backache, bone or joint pains, tremors, sensations of skin crawling or fasciculations. If signs or symptoms of withdrawal appear, the test is positive and no additional NARCAN should be administered.

Septic Shock

The optimal dosage of NARCAN or duration of therapy for the treatment of hypotension in septic shock patients has not been established (see **CLINICAL PHARMACOLOGY**).

Usage in Children

Opioid Overdose—Known or Suspected: The usual initial dose in children is 0.01 mg/kg body weight given I.V. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an I.V. route of administration is not available, NARCAN may be administered I.M. or S.C. in divided doses. If necessary, NARCAN can be diluted with sterile water for injection.

Postoperative Opioid Depression: Follow the recommendations and cautions under **Adult Postoperative Depres-**

Continued on next page

Narcan—Cont.

sion. For the initial reversal of respiratory depression, NARCAN should be injected in increments of 0.005 mg to 0.01 mg intravenously at two- to three-minute intervals to the desired degree of reversal.

Usage in Neonates

Opioid-induced Depression: The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines for postoperative opioid depression.

HOW SUPPLIED

NARCAN (naloxone hydrochloride injection, USP) for intravenous, intramuscular and subcutaneous administration is available as:

[See table at top of previous page]

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F). Protect from light.

Store in carton until contents have been used.

NARCAN® is a Registered Trademark of Endo Pharmaceuticals Inc.

Printed in U.S.A. 6487-01/Rev. Jan., 2001

NUBAIN®

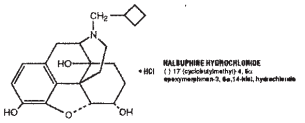
℞

[nū 'bān]

(Nalbuphine Hydrochloride)

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, oxymorphone.



NALBUPHINE HYDROCHLORIDE
• HCl (-)-17-(cyclobutylmethyl)-4,5α-epoxymorphinan-3,6α,14-diol, hydrochloride

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 hydrous, 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 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.

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.

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, oxymorphone, 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): Safe use of NUBAIN in pregnancy has not been established. Although animal reproductive studies have not revealed teratogenic or embryotoxic effects, nalbuphine should be administered to pregnant women only if clearly needed.

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 1:1.6. 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 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.

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, 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. 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.

Usage in Pregnancy

Teratogenic Effects

Pregnancy Category B—Reproduction studies have been performed in rabbits and in rats 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.

Use During Labor and Delivery

See **WARNINGS**.

Nursing Mothers

Limited data suggest that NUBAIN (nalbuphine hydrochloride) 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/clammy 99 (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 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.

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 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

NUBAIN 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. Drug abuse has been reported infrequently. Psychological and physical dependence and tolerance may follow the abuse or misuse of nalbuphine (see **WARNINGS**).

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 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.

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