NALBUPHINE HCI- nalbuphine hci injection, solution
HF Acquisition Co LLC, DBA HealthFirst

NALBUPHINE HCI INJ. 10mg/mL 10mL VIAL

SPL UNCLASSIFIED

Injection
Ampul
Fliptop Vial
Protect from light.

Rx only

BOXED WARNING

Life-Threatening Respiratory Depression - Serious, life-threatening, or fatal respiratory depression may occur with use of Nalbuphine Hydrochloride Injection, particularly when used concomitantly ...

WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION AND RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Nalbuphine Hydrochloride Injection, particularly when used concomitantly with other opioids or central nervous system depressants. Monitor for respiratory depression, especially during initiation of Nalbuphine Hydrochloride Injection or following a dose increase [see WARNINGS].

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see WARNINGS, PRECAUTIONS; DRUG INTERACTIONS].

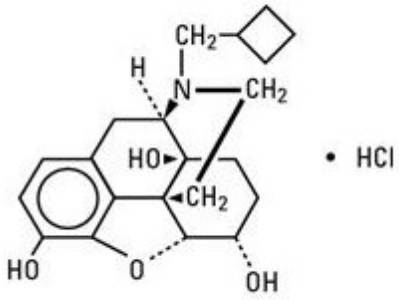
- Reserve concomitant prescribing of nalbuphine hydrochloride and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

CLOSE

DESCRIPTION

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. Chemically nalbuphine hydrochloride is 17-(cyclobutylmethyl)-4,5α-

epoxymorphinan-3,6α,14-triol hydrochloride. Nalbuphine hydrochloride molecular weight is 393.91 and is soluble in H2O (35.5 mg/mL at 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:



Nalbuphine Hydrochloride Injection is a sterile, nonpyrogenic solution of nalbuphine hydrochloride in water for injection. This product may be administered by subcutaneous, intramuscular or intravenous injection.

Each milliliter (mL) contains nalbuphine hydrochloride 10 mg or 20 mg; sodium citrate, dihydrate 0.47 mg and citric acid, anhydrous 0.63 mg added as buffers and may contain sodium hydroxide and/or hydrochloric acid for pH adjustment; pH 3.7 (3.0 to 4.5). Contains sodium chloride for tonicity adjustment.

Multiple-dose vials contain 1.8 mg/mL methylparaben and 0.2 mg/mL propylparaben added as preservatives. Single-dose products contain no bacteriostat or antimicrobial agent and unused portions must be discarded.

CLINICAL PHARMACOLOGY

Effects on the Endocrine System

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date.

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

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

Nalbuphine hydrochloride may produce the same degree of respiratory depression as equianalgesic doses of morphine. However, Nalbuphine Hydrochloride Injection 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.

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

INDICATIONS & USAGE

Nalbuphine Hydrochloride Injection is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. 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.

Limitations of Use

Because of the risks of addiction, abuse, and misuse, with opioids, even at recommended doses [see WARNINGS], reserve Nalbuphine Hydrochloride Injection for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]

Have not been tolerated, or are not expected to be tolerated
Have not provided adequate analgesia, or are not expected to provide adequate analgesia

CONTRAINDICATIONS

Nalbuphine Hydrochloride Injection is contraindicated in patients with:

Significant respiratory depression [see WARNINGS]
Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see WARNINGS]
Known or suspected gastrointestinal obstruction, including paralytic ileus [see WARNINGS]
Hypersensitivity to nalbuphine or to any of the other ingredients in Nalbuphine Hydrochloride Injection.

WARNINGS

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see OVERDOSAGE]. Carbon dioxide (CO2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Nalbuphine Hydrochloride Injection, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with and following dosage increases of Nalbuphine Hydrochloride Injection.

To reduce the risk of respiratory depression, proper dosing and titration of Nalbuphine Hydrochloride Injection is essential [see DOSAGE & ADMINISTRATION]. Overestimating the Nalbuphine Hydrochloride Injection dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper [see DOSAGE & ADMINISTRATION].

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Nalbuphine Hydrochloride Injection with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see PRECAUTIONS; Drug Interactions].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Nalbuphine Hydrochloride Injection is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see PRECAUTIONS; Drug Interactions and Information for Patients].

Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of Nalbuphine Hydrochloride Injection in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease

Nalbuphine Hydrochloride Injection-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of use of Nalbuphine Hydrochloride Injection [see WARNINGS].

Elderly, Cachectic, or Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see WARNINGS]. Monitor such patients closely, particularly when initiating and titrating Nalbuphine Hydrochloride Injection and when Nalbuphine Hydrochloride Injection is given concomitantly with other drugs that depress respiration [see WARNINGS]. Alternatively, consider the use of non-opioid analgesics in these patients.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than 1 month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

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.

Use in Ambulatory Patients

Nalbuphine Hydrochloride Injection 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 Injection effects that would affect driving or other potentially dangerous tasks.

Use in Pregnancy (Other Than Labor)

Severe fetal bradycardia has been reported when Nalbuphine Hydrochloride Injection 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. Avoid the use of Nalbuphine Hydrochloride Injection in pregnant women unless 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. Some of these events have been life-threatening. 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. Nalbuphine 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 nalbuphine has been used.

Addiction, Abuse, and Misuse

Nalbuphine hydrochloride is a synthetic opioid agonist-antagonist analgesic. As an opioid, Nalbuphine Hydrochloride Injection exposes users to the risks of addiction, abuse, and misuse [see DRUG ABUSE AND DEPENDENCE].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Nalbuphine Hydrochloride Injection. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing Nalbuphine Hydrochloride Injection. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

PRECAUTIONS

General

Impaired Renal or Hepatic Function

Because nalbuphine is metabolized in the liver and excreted by the kidneys, Nalbuphine Hydrochloride Injection should be used with caution in patients with renal or liver dysfunction and administered in reduced amounts.

Myocardial Infarction

As with all potent analgesics, Nalbuphine Hydrochloride Injection should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Tract Surgery

As with all opioid analgesics, Nalbuphine Hydrochloride Injection 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 Nalbuphine Hydrochloride Injection 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:

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications [see PRECAUTIONS; Drug Interactions].

Nalbuphine Hydrochloride Injection 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.
Nalbuphine Hydrochloride Injection is to be used as prescribed by a physician. Dose or frequency should not be increased without first consulting with a physician since Nalbuphine Hydrochloride Injection may cause psychological or physical dependence.
The use of Nalbuphine Hydrochloride Injection with other opioids can cause signs and symptoms of withdrawal.
Abrupt discontinuation of Nalbuphine Hydrochloride Injection after prolonged usage may cause signs and symptoms of withdrawal.

Laboratory Tests

Nalbuphine Hydrochloride Injection 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.

Drug Interactions

Benzodiazepines and other Central Nervous System (CNS) Depressants

Although Nalbuphine Hydrochloride Injection 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 Nalbuphine Hydrochloride Injection. Therefore, due to additive pharmacologic effects, the concomitant use of other opioid analgesics, benzodiazepines or other CNS depressants such as alcohol, other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, can increase the risk of respiratory depression, profound sedation, coma, and death.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see WARNINGS].

Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue), has resulted in serotonin syndrome [see PRECAUTIONS; Information for Patients].

If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Nalbuphine Hydrochloride Injection if serotonin syndrome is suspected.

Monoamine Oxidase Inhibitors (MAOIs)

MAOI (e.g., phenelzine, tranylcypromine, linezolid) interactions with opioids may manifest as serotonin syndrome [see Drug Interactions] or opioid toxicity (e.g., respiratory depression, coma [see Warnings]).

The use of Nalbuphine Hydrochloride Injection is not recommended for patients taking MAOIs or

within 14 days of stopping such treatment.

If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.

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 (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 Nalbuphine Hydrochloride Injection administration. The maximum recommend 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

Nalbuphine Hydrochloride Injection 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, Nalbuphine Hydrochloride Injection 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. Nalbuphine Hydrochloride Injection did not affect either male or female fertility rats.

Pregnancy

Teratogenic Effects

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.

Fetal/Neonatal Adverse Reactions

Severe fetal bradycardia has been reported when nalbuphine hydrochloride 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.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Nalbuphine Hydrochloride Injection is not recommended for use

in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including Nalbuphine Hydrochloride Injection, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Nursing Mothers

Limited data suggest that Nalbuphine Hydrochloride Injection is excreted in maternal milk but only in a small amount (less than 1% of the administered dose) and with a clinically insignificant effect.

Infants exposed to Nalbuphine Hydrochloride Injection through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

Pediatric Use

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

Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to Nalbuphine Hydrochloride Injection. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of Nalbuphine Hydrochloride Injection slowly in geriatric patients [see WARNINGS].

ADVERSE REACTIONS

The most frequent adverse reaction in 1066 patients treated in clinical studies with Nalbuphine Hydrochloride Injection 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. Some of these allergic reactions may be life-threatening. Other allergic-type reactions reported include stridor, bronchospasm, wheezing, edema, rash, pruritus,

nausea, vomiting, diaphoresis, weakness, and shakiness.

Events Observed during Post-marketing Surveillance of Nalbuphine Hydrochloride Injection

Due to the nature and limitations of spontaneous reporting, causality has not been established for the following adverse events received for Nalbuphine Hydrochloride Injection: abdominal pain, pyrexia, depressed level or loss of consciousness, somnolence, tremor, anxiety, pulmonary edema, agitation, seizures, and injection site reactions such as pain, swelling, redness, burning, and hot sensations. Death has been reported from severe allergic reactions to Nalbuphine Hydrochloride Injection treatment. Fetal death has been reported where mothers received Nalbuphine Hydrochloride Injection during labor and delivery.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

DRUG ABUSE AND DEPENDENCE

Abuse

Nalbuphine Hydrochloride Injection contains nalbuphine, which can be abused and is subject to misuse, addiction, and criminal diversion [see WARNINGS].

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating health care provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Nalbuphine Hydrochloride Injection, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of Nalbuphine Hydrochloride

Abuse of Nalbuphine Hydrochloride Injection poses a risk of overdose and death. The risk is increased with concurrent abuse of Nalbuphine Hydrochloride Injection with alcohol and other central nervous system depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Dependence

Both tolerance and physical dependence opioid therapy can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Nalbuphine Hydrochloride Injection should not be abruptly discontinued [see DOSAGE & ADMINISTRATION]. If Nalbuphine Hydrochloride Injection is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see PRECAUTIONS; Pregnancy].

OVERDOSAGE

Clinical Presentation

Acute overdose with Nalbuphine Hydrochloride Injection alone can be manifested by respiratory depression and dysphoria. Acute overdose with Nalbuphine Hydrochloride Injection and other opioids or CNS depressants can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to nalbuphine hydrochloride overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to Nalbuphine Hydrochloride Injection overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of nalbuphine, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms

experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

DOSAGE & ADMINISTRATION

Important Dosage and Administration Instructions

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.

Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see WARNINGS].

Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with Nalbuphine Hydrochloride Injection and adjust the dosage accordingly [see WARNINGS].

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

Initial Dosage

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 WARNINGS; Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants]. In nontolerant 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 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 Nalbuphine Hydrochloride Injection may be followed by respiratory depression which can be reversed with the opioid antagonist naloxone hydrochloride.

Titration and Maintenance of Therapy

Individually titrate Nalbuphine Hydrochloride Injection to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving nalbuphine hydrochloride to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [see WARNINGS]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the nalbuphine hydrochloride dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse events.

Discontinuation of Nalbuphine Hydrochloride Injection

When a patient who has been taking Nalbuphine Hydrochloride Injection regularly and may be physically dependent no longer requires therapy with Nalbuphine Hydrochloride Injection, taper the

dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue Nalbuphine Hydrochloride Injection in a physically-dependent patient [see WARNINGS, DRUG ABUSE AND DEPENDENCE].

HOW SUPPLIED

NALBUPHINE HCI INJ. is supplied in the following dosage forms.
NDC 51662-1420-1
NALBUPHINE HCI INJ. 10mg/mL 10mL VIAL

HF Acquisition Co LLC, DBA HealthFirst
Mukilteo, WA 98275

Also supplied in the following manufacture supplied dosage forms

Nalbuphine Hydrochloride Injection for intramuscular, subcutaneous, or intravenous use is a sterile solution available in:

Unit of Sale	Concentration
NDC 0409-1463-01 Tray of 10 – 1 mL Single-dose Ampuls	10 mg/ mL
NDC 0409-1465-01 Tray of 10 – 1 mL Single-dose Ampuls	20 mg/ mL
NDC 0409-1464-01 Case of 25 – 10 mL Multiple-dose Fliptop Vials	100 mg/10 mL (10 mg/ mL)
NDC 0409-1467-01 Case of 25 – 10 mL Multiple-dose Fliptop Vials	200 mg/10 mL (20 mg/ mL)

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]
Protect from excessive light. Store in carton until contents have been used.

SPL UNCLASSIFIED

Distributed by Hospira, Inc., Lake Forest, IL 60045 USA

LAB-0839-5.0

Revised: 06/2019

PRINCIPAL DISPLAY PANEL - VIAL LABELING

10 mL Multiple-dose

NALBUPHINE HCl Inj.

10 mg/mL

For I.V., I.M., or S.C. use.

HOSPIRA, INC.
LAKE FOREST, IL 60045 USA

NDC 0409-1464-01

Protect from light. Retain in carton until contents are used. Each mL contains nalbuphine HCl 10 mg; sodium citrate, dihyd. 0.47 mg and citric acid, anhyd. 0.63 mg added as buffers; methylparaben 1.8 mg, propylparaben 0.2 mg added as preservatives. NaCl added to adjust tonicity. May contain NaOH and/or HCl to adjust pH. Sterile, nonpyrogenic. Usual dosage: See insert. Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

RL-1219 (2/05)

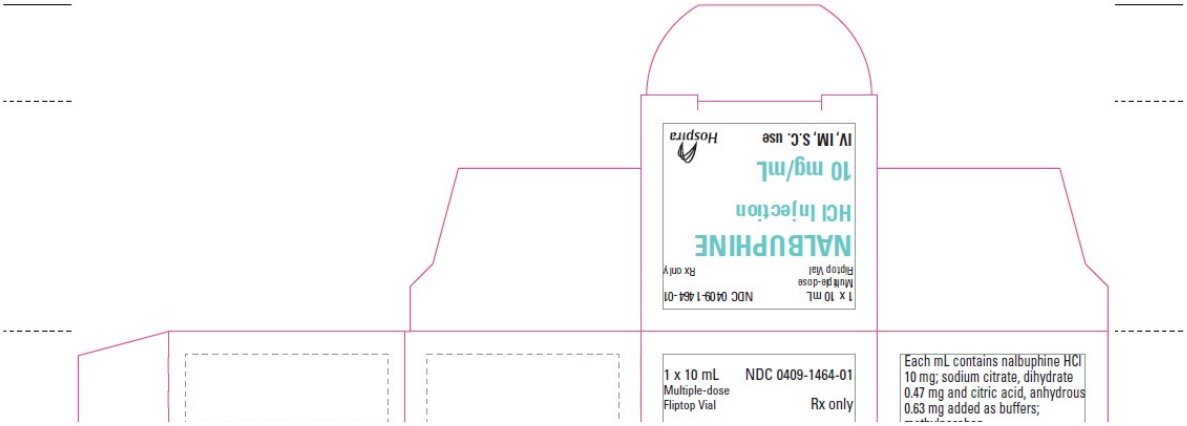
℞ only

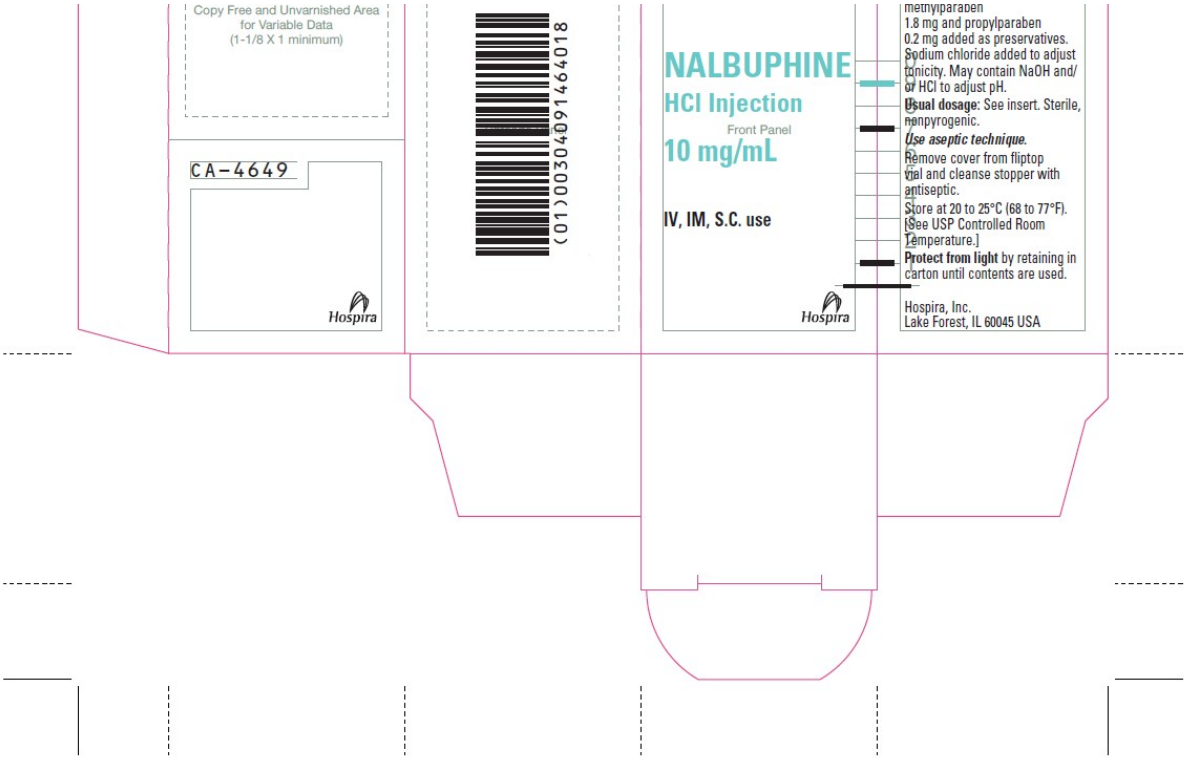
Hospira

PRINCIPAL DISPLAY PANEL- CARTON LABELING

CA-4649v1.pdf

PMS Black
PMS 325





SERIALIZED FOR 10mL
MOLDED FLIPTOP VIAL
FOLDING CARTON,
PRINTED FOR BOTTLES
(GLASS WITH ENCLOSURE)
1-5/16 X 1-5/16 X 2-7/16

Plant Line(s): RM 9

[redacted]

[redacted]

Pfizer GLOBAL SUPPLY

Hospira, A Pfizer Company
Lake Forest, IL 60045

DO NOT SCALE TEMPLATE

STUDIO NOTES:

1. Barcode to be located on the side panel. Barcode to be printed on a white background, background to extend 1/4 inch on each end of barcode (when space permits), at least 1/16 inch above barcode and at least 1/16 inch below human readable characters. Due to space constraints, a 7.5 mil/0.25 inch high barcode should be used.
4. For accumulated dimensions in a straight line: ±1/32 tol.
5. Perforations alternate typ. 3/32 crease 3/32 cut.

PRINCIPAL DISPLAY PANEL - SERIALIZED CARTON LABELING

NALBUPHINE HCI

nalbuphine hci injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:51662-1420(NDC:0409-1464)
Route of Administration	INTRAVENOUS, INTRAMUSCULAR, SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NALBUPHINE HYDROCHLORIDE (UNII: ZU4275277R) (NALBUPHINE - UNII:L2T84IQI2K)	NALBUPHINE HYDROCHLORIDE	10 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
METHYLPARABEN (UNII: A2I8C7HI9T)	1.8 mg in 1 mL
WATER (UNII: 059QF0KO0R)	
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)	0.47 mg in 1 mL
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)	0.63 mg in 1 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
PROPYLPARABEN (UNII: Z8IX2SC1OH)	0.2 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51662-1420-1	1 in 1 CARTON	10/29/2019	
1		10 mL in 1 VIAL, MULTI-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA070915	10/29/2019	

Labeler - HF Acquisition Co LLC, DBA HealthFirst (045657305)

Registrant - HF Acquisition Co LLC, DBA HealthFirst (045657305)

Establishment

Name	Address	ID/FEI	Business Operations
HF Acquisition Co LLC, DBA HealthFirst		045657305	relabel(51662-1420)