NALBUPHINE HYDROCHLORIDE
Injection
Ampul
Flintop Vial
Protect from light.

Rx only

**WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; and NEONATAL OPIOID WITHDRAWAL SYNDROME**

**Addiction, Abuse, and Misuse**
Nalbuphine hydrochloride injection exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient’s risk prior to prescribing nalbuphine hydrochloride injection, and monitor all patients regularly for the development of these behaviors or conditions [see WARNINGS].

**Life-Threatening Respiratory Depression**
Serious, life-threatening, or fatal respiratory depression may occur with use of nalbuphine hydrochloride injection. Monitor for respiratory depression, especially during initiation of nalbuphine hydrochloride injection or following a dose increase [see WARNINGS].

**Neonatal Opioid Withdrawal Syndrome**
Prolonged use of nalbuphine hydrochloride injection during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see WARNINGS].

**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 Structural Formula](image)
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

Nalbuphine hydrochloride 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 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 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 mu agonist opioid analgesics (e.g., morphine, oxymorphone, fentanyl), nalbuphine hydrochloride may partially reverse or block opioid-induced respiratory depression from the mu agonist analgesic. Nalbuphine hydrochloride may precipitate withdrawal in patients dependent on opioid drugs. Nalbuphine hydrochloride should be used with caution in patients who have been receiving mu opioid analgesics on a regular basis.

INDICATIONS AND USAGE

Nalbuphine hydrochloride injection is indicated for the management of moderate to pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Nalbuphine hydrochloride 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 for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]

- 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]
- Should not be administered to patients who are hypersensitive to nalbuphine hydrochloride, or to any of the other ingredients in nalbuphine hydrochloride injection.

WARNINGS
Addiction, Abuse, and Misuse
Nalbuphine hydrochloride is a synthetic opioid agonist-antagonist analgesic. As an opioid, nalbuphine hydrochloride 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. 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 prior to prescribing nalbuphine hydrochloride, and monitor all patients receiving nalbuphine hydrochloride for the development of these behaviors or conditions. 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. Patients at increased risk may be prescribed opioids such as nalbuphine hydrochloride, but use in such patients necessitates intensive counseling about the risks and proper use of nalbuphine hydrochloride along with intensive monitoring for signs of addiction, abuse, and misuse.

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. 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.

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 OVERDOSEAGE]. 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, 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.

To reduce the risk of respiratory depression, proper dosing and titration of nalbuphine hydrochloride are essential [see DOSAGE AND ADMINISTRATION]. Overestimating the nalbuphine hydrochloride dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.
Neonatal Opioid Withdrawal Syndrome
Prolonged use of nalbuphine hydrochloride during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see PRECAUTIONS; Information for Patients, Pregnancy].

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

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

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 effects that would affect driving or other potentially dangerous tasks.

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

Use During Labor and Delivery
The placental transfer of nalbuphine is high, rapid, and variable with a maternal to fetal ratio ranging from 1:0.37 to 1:6. Fetal and neonatal adverse effects that have been reported following the administration of nalbuphine to the mother during labor include fetal bradycardia, respiratory depression at birth, apnea, cyanosis, and hypotonia. 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.

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

**Risks due to Interaction With Central Nervous System Depressants**

Hypotension, profound sedation, respiratory depression, coma, and death may result if nalbuphine hydrochloride is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., benzodiazepines and other sedatives/hypnotics, anxiolytics, and tranquillizers, muscle relaxants, general anesthetics, antipsychotics, other opioids).

When considering the use of nalbuphine hydrochloride in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient’s response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient’s use of alcohol or illicit drugs that can cause CNS depression. If the decision to begin nalbuphine hydrochloride is made, start with a lower dosage of nalbuphine hydrochloride, monitor patients for signs of respiratory depression, sedation, and hypotension, and consider using a lower dose of the concomitant CNS depressant [see PRECAUTIONS; Drug Interactions].

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

The use of nalbuphine hydrochloride 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-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 [see WARNINGS].

*Elderly, Cachetic, 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 and when nalbuphine hydrochloride 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.
PRECAUTIONS

General

Impaired Renal or Hepatic Function: Because nalbuphine is metabolized in the liver and excreted by the kidneys, nalbuphine hydrochloride 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 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 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:

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

Laboratory Tests

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

Addiction, Abuse, and Misuse

Inform patients that the use of nalbuphine hydrochloride, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see WARNINGS]. Instruct patients not to share nalbuphine hydrochloride with others and to take steps to protect nalbuphine hydrochloride from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting nalbuphine hydrochloride or when the dosage is increased, and that it can occur even at recommended dosages [see WARNINGS]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Interactions with CNS Depressants

Inform patients that potentially serious additive effects may occur if nalbuphine hydrochloride is used with CNS depressants and to seek medical attention if they experience increased sedation or difficulty breathing [see WARNINGS, PRECAUTIONS; Drug Interactions].
Serotonin Syndrome
Inform patients that nalbuphine hydrochloride 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]

Pregnancy

Neonatal Opioid Withdrawal Syndrome
Inform patients that prolonged use of nalbuphine hydrochloride during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [see WARNINGS, PRECAUTIONS; Pregnancy]

Embryo-Fetal Toxicity
Inform female patients of reproductive potential that nalbuphine hydrochloride can cause fetal harm and to inform the prescriber of a known or suspected pregnancy [see PRECAUTIONS; Pregnancy].

Lactation
Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs [see PRECAUTIONS; Nursing Mothers].

Drug Interactions

Central Nervous System Depressants
Due to additive pharmacologic effect, the concomitant use of CNS depressants such as alcohol, benzodiazepines and other sedative hypnotics, anxiolytics, and tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.

Consider dose reduction of one or both drugs. Monitor patients for signs of respiratory depression, sedation, and hypotension [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 effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), 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 if serotonin syndrome is suspected.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Infertility
Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see ADVERSE REACTIONS].
Pregnancy

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [see WARNINGS].

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 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, 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

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for nalbuphine hydrochloride and any potential adverse effects on the breastfed infant from nalbuphine hydrochloride or from the underlying maternal condition.

Infants exposed to nalbuphine hydrochloride 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. 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 slowly in geriatric patients [see WARNINGS].

ADVERSE REACTIONS

The most frequent adverse reaction in 1066 patients treated 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 treatment. Fetal death has been reported where mothers received nalbuphine hydrochloride during labor and delivery.

**Postmarketing Experience**

- serotonin syndrome
- adrenal insufficiency

**Androgen deficiency**

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as symptoms of hypogonadism, such as impotence, erectile dysfunction, or amenorrhea. The causal role of opioids in the 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. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

**DRUG ABUSE AND DEPENDENCE**

**Abuse**

Nalbuphine hydrochloride is a substance with a high potential for abuse similar to other opioids. Nalbuphine hydrochloride 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, 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.

**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 should not be abruptly discontinued [see DOSAGE AND ADMINISTRATION]. If nalbuphine hydrochloride 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 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 overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of nalbuphine hydrochloride in nalbuphine hydrochloride, 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 begun with care and by titration with smaller than usual doses of the antagonist.

**DOSAGE AND ADMINISTRATION**

**Important Dosage and Administration Instructions**

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 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 due to Interactions with Central Nervous System 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 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**

When a patient who has been taking nalbuphine hydrochloride regularly and may be physically dependent no longer requires therapy with nalbuphine hydrochloride, use a gradual downward titration of the dosage to prevent signs and symptoms of withdrawal. Do not stop nalbuphine hydrochloride abruptly [see WARNINGS, DRUG ABUSE AND DEPENDENCE].

**HOW SUPPLIED**

Nalbuphine Hydrochloride Injection is supplied as follows:

<table>
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<th>NDC No.</th>
<th>Container</th>
<th>Size (mL)</th>
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<td>Ampul</td>
<td>1</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>0409-1465-01</td>
<td>Ampul</td>
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<td>20</td>
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<tr>
<td>0409-1464-01</td>
<td>Fliptop Vial</td>
<td>10</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>(multiple-dose)</td>
<td></td>
<td></td>
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<tr>
<td>0409-1467-01</td>
<td>Fliptop Vial</td>
<td>10</td>
<td>20</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>(multiple-dose)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

**Protect from light.** Store in carton until contents have been used.

Revised: 4/2016

EN-4249

Hospira, Inc., Lake Forest, IL 60045 USA