PRODUCT MONOGRAPH

©NUBAIN

(Nalbuphine Hydrochloride)

Injection, 10 mg/mL

Opioid Analgesic
Adjunct Anesthetic

Sandoz Canada Inc.
145 Jules-Léger
Boucherville, Quebec, J4B 7K8

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(nalbuphine hydrochloride)
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneously, intramuscularly or intravenously	Solution for injection	Sodium chloride, sodium citrate dihydrate, citric acid and water for injection. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

NUBAIN (nalbuphine hydrochloride) is indicated for the relief of moderate to severe pain.

NUBAIN can also be used as a supplement to surgical anesthesia, an adjunct to preoperative and postoperative analgesia, and obstetrical analgesia during labor and delivery.

Geriatrics (> 65 years of age)
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

Pediatrics (< 18 years of age):
The safety and efficacy of nalbuphine has not been studied in the pediatric population. Therefore the use of NUBAIN is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

NUBAIN (nalbuphine hydrochloride) should not be administered to

- Patients who are hypersensitive to the active substance nalbuphine or other opioid analgesics or to any ingredients in the formulation. For a complete listing, see the

DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding or pregnant (see Serious Warnings and Precautions, and Warnings and Precautions).

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with parenteral opioid formulations, NUBAIN should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

As with other CNS depressants, patients who have received NUBAIN should have appropriate surveillance. Resuscitative equipment and a narcotic antagonist such as naloxone should be readily available to manage apnea.

Addiction, Abuse, and Misuse

NUBAIN poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing NUBAIN, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). NUBAIN should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression may occur with use of NUBAIN. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of NUBAIN or following a dose increase. Further, instruct patients of the hazards related to taking opioids including fatal overdose

Accidental Exposure
Accidental exposure of even one dose of NUBAIN, especially by children, can result in a fatal overdose of nalbuphine hydrochloride (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of NUBAIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

Interaction with Alcohol
The co-ingestion of alcohol with NUBAIN should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

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 AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of NUBAIN 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.**

General
Patients should be instructed not to give NUBAIN (nalbuphine hydrochloride) to anyone other than for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. NUBAIN should be stored securely to avoid theft or misuse.

NUBAIN should only be administered by persons knowledgeable in the continuous delivery of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

NUBAIN should be administered as a supplement to surgical 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.

Patients should be cautioned not to consume alcohol while taking NUBAIN as it may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further dose increase of nalbuphine can occur at particularly high doses. A nalbuphine dose reduction or change in opioid may be required.

Abuse and Misuse
Like all opioids, NUBAIN is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, NUBAIN should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as NUBAIN, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Carcinogenesis and Mutagenesis
See TOXICOLOGY section.

Cardiovascular
NUBAIN administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of NUBAIN.

The use of NUBAIN in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression and should be avoided (see DOSAGE AND ADMINISTRATION).

Myocardial Infarction: As with all potent analgesics, NUBAIN should be used with caution in patients with myocardial infarction who have nausea or vomiting. Hemodynamic studies in patients with severe arteriosclerotic heart changes reveal that

NUBAIN has circulatory effects similar to those of morphine, i.e., a minimal decrease in oxygen consumption, cardiac index, left ventricular end-diastolic pressure and cardiac work.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of NUBAIN and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

Use in Drug and Alcohol Addiction:

NUBAIN is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to NUBAIN; extreme caution and awareness is warranted to mitigate the risk.

Endocrine

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

Gastrointestinal Effects

NUBAIN and other morphine-like opioids have been shown to decrease bowel motility. Nalbuphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see CONTRAINDICATIONS).

Hepatic/Biliary/Pancreatic
Biliary Tract Surgery: NUBAIN may cause spasm of the sphincter of Oddi. It is not recommended to be used for analgesia in patients with acute abdominal conditions. It should only be used for anesthesia in these patients when its benefits outweigh its potential risks.

Neonatal Opioid Withdrawal Syndrome (NOWS)
Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

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.

Use of NUBAIN is contraindicated in pregnant women (see CONTRAINDICATIONS).

Neurologic
Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): NUBAIN should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

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 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 NUBAIN 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 DRUG INTERACTIONS).

NUBAIN should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see CONTRAINDICATIONS and ADVERSE REACTIONS, Sedation, and DRUG INTERACTIONS).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

Head Injury: The respiratory depressant effects of nalbuphine, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, nalbuphine may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, nalbuphine must be used with extreme caution and only if it is judged essential (see CONTRAINDICATIONS).

Use in Patients with Convulsive or Seizure Disorders: The nalbuphine hydrochloride in NUBAIN may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Therefore, NUBAIN should not be used in these patients (see CONTRAINDICATIONS).

Serotonin syndrome: NUBAIN could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotonergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. NUBAIN should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see DRUG INTERACTIONS).

Peri-Operative Considerations

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

In the case of planned chordotomy or other pain-relieving operations, patients should not

be treated with NUBAIN for at least 24 hours before the operation and NUBAIN should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

Nalbuphine and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Psychomotor Impairment

NUBAIN may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of nalbuphine with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

Renal

Impaired Renal or Hepatic Function: Because NUBAIN is metabolized in the liver and excreted by the kidneys, patients with renal or liver dysfunction may show an exaggerated response to customary doses. In these individuals, NUBAIN should be used with caution and administered in reduced amounts.

Respiratory

Respiratory Depression: Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, 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. Nalbuphine should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see CONTRAINDICATIONS).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of NUBAIN the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with NUBAIN and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

To reduce the risk of respiratory depression, proper dosing and titration of NUBAIN are

essential. Overestimating the NUBAIN dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups, and DOSAGE AND ADMINISTRATION).

Use in Patients with Chronic Pulmonary Disease: Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with NUBAIN, as in these patients, even usual therapeutic doses of NUBAIN may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of NUBAIN is contraindicated in Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see CONTRAINDICATIONS).

Sexual Function/Reproduction

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Special Populations

Special Risk Groups: Nalbuphine should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture

Pregnant Women: Studies in humans have not been conducted. NUBAIN crosses the placental barrier and is contraindicated in pregnant women.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal Opioid Withdrawal Syndrome (NOWS), unlike opioid withdrawal syndrome in adults, may be life-threatening (see WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS), ADVERSE REACTIONS, Post-Marketing Experience).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

Labour, Delivery and Nursing Women: Since opioids can cross the placental barrier and are excreted in breast milk, NUBAIN is contraindicated in nursing women and is not recommended to be used during labour and delivery unless, in the judgement of the physician, the potential benefits outweigh the risks. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a

drug that counters the effects of opiates, should be readily available if NUBAIN is used in this population.

The placental transfer of nalbuphine is high, relatively rapid and variable with a maternal to fetal ratio ranging from 1:0.37 to 1:6.03. Fetal and neonatal adverse effects that have been reported following the administration of nalbuphine to the mother during labour include fetal bradycardia, respiratory depression at birth, apnea, cyanosis, and hypotonia. 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.

Pediatrics (< 18 years of age): The safety and efficacy of NUBAIN have not been studied in the pediatric population. Therefore, use of NUBAIN is not recommended in patients under 18 years of age.

Geriatrics (> 65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of NUBAIN (nalbuphine hydrochloride) injection are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

The following adverse effects occur less frequently with opioid analgesics and include those reported in NUBAIN clinical trials, whether related or not to nalbuphine hydrochloride.

In clinical trials with NUBAIN (nalbuphine hydrochloride) the most frequently reported side effects were: sedation (36% of 1066), sweating or clammy (9%), nausea or vomiting (6%), dizziness or vertigo (5%), dry mouth (4%) and headache (3%).

Less Common Clinical Trial Adverse Drug Reactions:

Central Nervous System: nervousness, crying, depression, restlessness, euphoria, hostility, confusion, faintness, floating, unusual dreams, numbness, feeling of heaviness, and psychotomimetic effects such as hallucinations, feeling of unreality and dysphoria. 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.

Respiration: Depression, dyspnea, asthma.

Dermatological: 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 with patients using NUBAIN include stridor, bronchospasm, wheezing, edema, rash, pruritis, 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.

Androgen deficiency: 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. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

DRUG INTERACTIONS

Overview

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants (including alcohol):
Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases 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 AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment). NUBAIN should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Drug-Drug Interactions

Central Nervous System (CNS) Depressants : Both magnitude and duration of CNS and cardiovascular effects may be enhanced when NUBAIN is administered to patients

receiving barbiturates, benzodiazepines, neuroleptics, halogenic gases and other non-selective CNS depressants (e.g. alcohol). When patients have received such drugs, the dose of NUBAIN required will be less than usual. Likewise, following the administration of NUBAIN the dose of other CNS-depressant drugs should be reduced.

MAO Inhibitors: It is usually recommended to discontinue MAO inhibitors 2 weeks prior to any surgical or anesthetic procedure.

Serotonergic Agents: Coadministration of nalbuphine with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see WARNINGS AND PRECAUTIONS, Neurologic).

Drug-Lifestyle Interactions

The concomitant use of alcohol should be avoided (see WARNINGS AND PRECAUTIONS, General).

Drug-Laboratory Interactions

Monitoring and Laboratory Tests: NUBAIN may interfere with enzymatic methods for the detection of opioids depending on the specificity and sensitivity of the laboratory tests. Please consult the test manufacturer for specific details.

DOSAGE AND ADMINISTRATION

Dosing Considerations

NUBAIN (nalbuphine hydrochloride) injection should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see WARNINGS AND PRECAUTIONS, Peri-operative Considerations).

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression.

For acute pain, it is recommended that NUBAIN be used for a maximum of 7 days at the lowest dose that provides adequate pain relief.

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. If NUBAIN is used for more than 7 days for the management of chronic non-cancer, non-palliative pain, it is recommended that 90 mg (90 morphine milligram equivalent) of NUBAIN not be exceeded. Each patient should be assessed for their risk prior to prescribing NUBAIN as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of NUBAIN (see DOSAGE AND ADMINISTRATION, Adjustment or reduction of Dosage).

Analgesia

The usual recommended adult dose of NUBAIN (nalbuphine hydrochloride) is 10 mg for a 70 kg individual, administered subcutaneously, intramuscularly or intravenously. This dose may be repeated every 3 to 6 hours as required. In non-tolerant individuals, the recommended dosage range is 10 mg to 20 mg, with a maximum single dose of 20 mg and a maximum total daily dose of 160 mg. Dosage should be adjusted according to the severity of the pain, physical status of the patient, and other medications which the patient may be receiving (see Interaction with Other Central Nervous System Depressants under WARNING).

Recommended Dose and Dosage Adjustment

Opioid Rotation: Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other factors. When switching from one opioid to another, consider reducing the calculated dose by 25-50% to minimize the risk of overdose. Subsequently, up-titrate the dose, as required, to reach the appropriate maintenance dose.

Opioid Analgesics - Approximate Analgesic Equivalences[1]

Drug	Equivalent Dose (mg)[2] [compared to morphine 10 mg IM]		Duration of Action (hours)
	Parenteral	Oral	
Strong Opioid Agonists			
Morphine (single dose)	10	60[3]	3 - 4
Oxycodone	15	30[4]	2 – 4
Hydromorphone	1.5	7.5	2 - 4
Anileridine	25	75	2 - 3
Levorphanol	2	4	4 - 8
Meperidine[6]	75	300	1 - 3
Oxymorphone	1.5	5 (rectal)	3 – 4
Methadone[5]	-	-	-
Heroine	5 – 8	10 – 15	3 – 4
Weak Opioid Agonists			
Codeine	120	200	3 – 4
Propoxyphene	50	100	2 – 4
Mixed Agonist- Antagonists[7]			
Pentazocine[6]	60	180	3 – 4
Nalbuphine	10	-	3 – 6
Butorphanol	2	-	3 – 4

Footnotes:

[1]References:

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Cherny NI, Portenoy RK. Practical issues in the management of cancer pain. In: Wall PD, Melzack R, editors. Textbook of pain. 3rd ed. New York: Churchill Livingstone; 1994. p. 1437-67.

[2] **Most of the data were derived from single-dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain. As analgesic conversion factors are approximate and patient response may vary, dosing should be individualized according to relief of pain and side effects. Because of**

incomplete cross-tolerance, dose reductions of 25% to 50% of the equianalgesic dose may be appropriate in some patients when converting from one opioid to another, particularly at high doses.[†] Upward titration may be required to reach appropriate maintenance doses.

[†]Levy MH. Pharmacologic treatment of cancer pain. N Engl J Med 1996;335:1124-1132.

[3] **For acute pain, the oral or rectal dose of morphine is six times the injectable dose. However, for chronic dosing, clinical experience indicates that this ratio is 2-3:1 (i.e., 20-30 mg of oral or rectal morphine is equivalent to 10 mg of parenteral morphine).**

[4] Based on single entity oral oxycodone in acute pain.

[5] Extremely variable equianalgesic dose. Patients should undergo individualized titration starting at an equivalent to 1/10 of the morphine dose.

[6] Not recommended for the management of chronic pain.

[7] Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

Patients with Hepatic Impairment:
Patients with liver dysfunction may show an exaggerated response to customary doses. In these individuals, NUBAIN should be used with caution and administered in reduced amounts

Patients with Renal Impairment:
Patients with renal dysfunction may show an exaggerated response to customary doses. In these individuals, NUBAIN should be used with caution and administered in reduced amounts.

Geriatrics: Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. NUBAIN should be initiated at a low dose and slowly titrated to effect (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Use with Non-Opioid Medications: If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. NUBAIN can be safely used concomitantly with usual doses of other non-opioid analgesics.

Dose Titration: Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects**.

Dosage adjustments should be based on the patient's clinical response.

Adjustment or Reduction of Dosage: Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including NUBAIN. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Following successful relief of moderate to severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see WARNINGS AND PRECAUTIONS). Tapering should be individualised and carried out under medical supervision.

Patients should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Balanced Anesthesia
Balanced anesthesia with NUBAIN requires larger doses than for the multiple doses recommended above for analgesia. Induction schedules with NUBAIN range from 0.3 mg/kg to 5 mg/kg intravenously over a 10 to 15 minute period.

After induction with NUBAIN is completed, maintenance doses of 0.25 mg/kg to 0.5 mg/kg can be used as required in single doses. Significant respiratory depression at the end of anesthesia rarely occurs with proper use of NUBAIN. Naloxone remains the specific antidote for any respiratory depression.

As a component to regional anesthesia, NUBAIN can be used in doses of 0.2 mg/kg to 0.5 mg/kg of body weight. NUBAIN produces sedation and additional analgesia to such regional techniques as alveolar nerve block and can be an adjunct to spinal anesthesia, regional nerve blocks, block of extremities, etc.

Incompatibility With Other Therapeutic Agents
NUBAIN is physically incompatible with nafcillin and ketorolac. Solutions of these drugs should not be mixed.

Disposal
NUBAIN should be kept in a safe place, out of the sight and reach of children before, during and after use. NUBAIN should never be disposed of in trash. Disposal via a pharmacy take back program is recommended. Unused or expired NUBAIN should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others.

Missed Dose
If a dose has been missed, the next dose should be administered at the next scheduled time and in the normal amount.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre for the most current information.

Symptoms

These are expected to be similar to those of other drugs of this class. The administration of single I.M. doses of 72 mg of NUBAIN to eight normal subjects has been reported to have resulted primarily in symptoms of sleepiness and mild dysphoria.

Treatment

Naloxone hydrochloride administered intravenously is a specific antidote for NUBAIN. Since the duration of action of NUBAIN may exceed that of naloxone, the patient should be kept under continued surveillance and repeated doses of naloxone should be administered as necessary. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

ACTION AND CLINICAL PHARMACOLOGY

NUBAIN (nalbuphine hydrochloride) is a synthetic opioid agonist-antagonist analgesic for parenteral use, related chemically to the opioid oxymorphone, and to the opioid antagonist naloxone. Nalbuphine has an analgesic (agonist action) potency equivalent to that of morphine on a milligram for milligram basis. Receptor studies show that nalbuphine binds to mu, kappa, and delta receptors, but not to sigma receptors. Nalbuphine is primarily a kappa agonist/ mu antagonist analgesic. The onset of action of nalbuphine 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 five hours and in clinical studies the duration of analgesic activity has been reported to range from three to six hours. The narcotic antagonist activity of NUBAIN is one-fourth as potent as that of nalorphine and ten times that of pentazocine.

At the usual adult dose of 10 mg / 70 kg, nalbuphine may produce respiratory depression equivalent to that of 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.

Nalbuphine 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 may partially reverse or block opioid-induced respiratory depression from the mu agonist analgesic. Nalbuphine may precipitate withdrawal in patients dependent on opioid drugs. Nalbuphine should be used with caution in patients who have been receiving mu opioid analgesics on a regular basis.

Central Nervous System: Nalbuphine produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in

the responsiveness of the brain stem centres to increases in CO2 tension and to electrical stimulation.

Nalbuphine depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Nalbuphine causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone overdose.

Gastrointestinal Tract and Other Smooth Muscle: Nalbuphine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System: Nalbuphine by may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

Endocrine System: Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

Immune System: In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

STORAGE AND STABILITY

Store at controlled room temperature (15°c to 30°c). Protect from excessive light. Store in carton until contents have been used.

SPECIAL HANDLING INSTRUCTIONS

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

NUBAIN (10.0 mg/mL) 1 mL Ampoule: Each mL contains 10.0 mg nalbuphine hydrochloride, 2.0 mg sodium chloride, 9.41 mg sodium citrate dihydrate, 12.62 mg citric acid and water for injection; pH adjusted with hydrochloric acid.

NUBAIN is available in 1 mL ampoules, boxes of 2 x 5 ampoules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

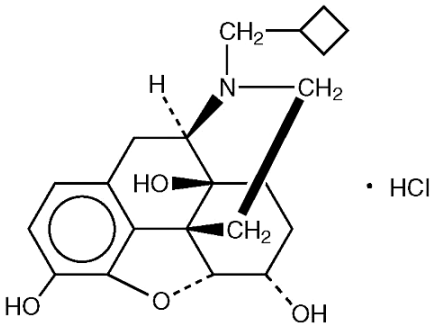
Proper name: nalbuphine hydrochloride

Chemical name: 17- (cyclobutylmethyl)-4,5-epoxy-, morphinan - 3,6,14-triol, hydrochloride

Molecular formula $C_{21}H_{27}NO_4 \bullet HCl$

Molecular mass: 393.91 g/mol

Structural formula:



Physicochemical properties: NUBAIN (nalbuphine hydrochloride) is a synthetic narcotic agonist-antagonist analgesic of the phenanthrene series. It is chemically related to both the widely used narcotic antagonist, naloxone, and the potent narcotic analgesic, oxymorphone, The pH is adjusted with hydrochloric acid. Nalbuphine hydrochloride is soluble in H_2O (35.5 mg/mL at 25°C) and ethanol (0.8%); insoluble in $CHCl_3$ and ether. Nalbuphine hydrochloride has pKa values of 8.71 and 9.96

NUBAIN (nalbuphine hydrochloride) is a Schedule G (Controlled) drug.

CLINICAL TRIALS

Animal tests show that parenterally administered nalbuphine HCI is an analgesic of the agonist-antagonist type. When administered subcutaneously in the mouse antiphenylquinone writhing tests nalbuphine hydrochloride, at the time of peak activity, was 2.3 times as potent as morphine sulfate 8.3 times as potent as codeine phosphate and 3.5 times as potent as pentazocine hydrochloride. In the same tests, orally administered nalbuphine, at peak activity time, was 0.27 times as potent as morphine, about equipotent with codeine, and 2.4 times as potent as pentazocine.

The onset of the analgesic effect of nalbuphine, codeine, and morphine by the subcutaneous route in mice was prompt; the peak time of the effect was similar for the three drugs. The duration of the effect of nalbuphine was the same as that of codeine, but morphine lasted longer. Orally, the onset of the analgesic effect of nalbuphine, codeine and morphine in mice was prompt. The peak times of effect for both nalbuphine and codeine were 5 minutes after administration, and the morphine peak time was after 20 minutes. The duration of the effect of all three drugs was similar.

Nalbuphine resembled known narcotic antagonists in several other tests. Administered subcutaneously, it blocked the oxymorphone, etonitazine and morphine-induced Straub tail response in mice, and oxymorphone-induced loss of righting reflex in rats. Oral nalbuphine also blocked the induction of oxymorphone-induced Straub tail response in mice. When administered subcutaneously to mice, nalbuphine was about three times as potent as an agonist than as an antagonist, based upon the results of the antiphenylquinone test for antagonist activity and upon the blockage of morphine-induced Straub tail response for antagonist activity.

Nalbuphine's predominant component, the alpha epimer, was 9.4 times as active as the beta epimer as an analgesic (in the mouse antiphenylquinone writhing test), 1.9 times as active as a narcotic antagonist (in blocking morphine-induced Straub tail response in mice), when tested subcutaneously. The beta epimer appeared to be qualitatively similar to the alpha epimer in its analgesic and narcotic antagonist actions but was quantitatively less potent.

TOXICOLOGY

Acute Toxicology: The animals which died within 14 days of dosing: mouse 1240 mg/kg (S.C.), 775 mg/kg (I.M.), 490 mg/kg (I.V.); rat: >1000 mg/kg (S.C.), 1200-1240 mg/kg (I.M.), 182-218 mg/kg (I.V.); dog: 200 mg/kg (S.C.), ~140 mg/kg (I.V.).

Depending on species and route of administration, the animals died either during clonic-tonic convulsions, in respiratory failure following clonic-tonic convulsions, or in respiratory failure without prior convulsions. Deaths generally occurred rapidly, and always within 72 hours of dosing. Other signs included cyanosis, depression, emesis, piloerection, ptosis, rapid or laboured respiration, salivation and tremor. Surviving

animals generally appeared normal within 24 hours of dosing and most signs had disappeared within 2 to 4 hours. There were no obvious sex differences in response to the drug. Other than skin sores at subcutaneous and intramuscular injection sites, there were no drug-induced abnormalities at autopsy.

Subacute Toxicology: Nalbuphine HCI was administered subcutaneously to groups of 20 male and 20 female young rats for two weeks (14 daily injections in 16 days) at dosage levels of 0, 6.6, 20 and 100 mg/kg/day. The only evidence of toxicity was decreased body weight at high dosage level. Some local irritation was observed at the injection site, but this was apparently due to repeated injections in the same area. Nalbuphine HCI was administered subcutaneously to groups of male and two female young adult beagles for two weeks (14 daily injections in 15 days) at dosage levels of 0, 2, 4, and 50 mg/kg/day. At the high dosage level, the signs of toxicity were slight weight loss, slight tremoring and hind-limb weakness, slight salivation and a few occurrences of emesis. Except for some mild local irritation at the injection sites in the 50 mg/kg/day group, due to large volumes of a 20 mg/ml drug solution, there were no other signs of toxicity. When nalbuphine HCI was administered intravenously to groups of three male and three female young adult beagle dogs once a day, 7 days a week for at least 2 weeks at dosage levels of 4, 8, and 32 mg/kg/day, there were no significant signs of toxicity.

Chronic Toxicology: Nalbuphine HCI was administered subcutaneously to starting groups of 35 male and 35 female young adult rats once a day, seven days a week for up to six months at dosage levels of 0, 7, 14 and 56 mg/kg/day. There was an interim sacrifice of 15 males and 15 females after three months. The drug caused a slight reduction in body weight gain, a slight to moderate increase in food consumption and decrease in food efficiency, a slight to marked but reversible hair loss and a slight normochromic, normocytic anemia, depending on the dosage level, frequency of dosing and animal's sex. Nalbuphine HCI was administered subcutaneously to groups of four male and four female adult beagle dogs once a day, seven days a week for six months at dosage levels of 0, 4, 8, and 50 mg/kg/day. The drug caused weight loss at all dosage levels.

Carcinogenesis and Mutagenesis: 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 induces an increased frequency of mutation in mouse lymphoma cells.

Reproduction and Teratology: The reproductive effects of parenterally administered nalbuphine HCI were evaluated in 1) a Segment I fertility and general reproductive performance study in rats at subcutaneous dosage levels of 14, 28 and 56 mg/kg/day, 2) a Segment II teratology study in rats at subcutaneous dosage levels of 7, 14, and 100 mg/kg/day and in rabbits at intravenous dosage levels of 4, 8 and 32 mg/kg/day, and 3) a Segment III perinatal-postnatal study in rats at subcutaneous dosage levels of 14, 28 and 56 mg/kg/day. No adverse effects of compound administration were observed during the

evaluation of fertility and general reproductive performance and there was no evidence of compound-induced embryotoxicity or teratogenesis.

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.

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.

Local Irritation Study: A solution of nalbuphine HCI (10 mg/ml) was tested for local irritation by high subcutaneous injection in the shaved abdomen of young mice. Both the 24- and 48- hour readings showed only slight irritation.

Special Studies – Distant Alopecia: The purpose of these studies was to determine the maximum "no-effect" dosage level for distant hair loss in rats and dogs. Nalbuphine hydrochloride was administered subcutaneously to groups of 35 male and 35 female rats at dosages of 0.1 to 56 mg/kg/day. The number of rats exhibiting alopecia increased with increases in dosage, but never exceeded 44 % (at the highest dose level of 56 mg/kg/day). The onset of alopecia was not dose-related or dose-related or dose-dependent (appearing within the first 3 weeks) and the time to peak effect was generally from 3 to 12 weeks. The degree of alopecia ranged from slight to marked and was seen on the abdomen, chest, back, neck, sides, limbs, paw, hip, shoulders and head. The threshold dose was estimated to be 0.16 mg/kg/day.

Dose of 0.1 to 50 mg/kg/day were administered subcutaneously to groups of four male and four female beagle dogs once daily for 1-1/2 to 2-1/2 months. Alopecia was seen at all dosage levels, including the controls, and its incidence increased with dose. All animals in the 4 mg/kg/day group exhibited alopecia. The onset of alopecia was dose-related and generally occurred within eight weeks. The degree of alopecia ranged from slight to marked and was seen on the abdomen, muzzle, chest, ears, limbs, neck, forehead, and tail. The threshold dose for alopecia was estimated to be 0.09 mg/kg/day.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

© NUBAIN
(nalbuphine hydrochloride)
Injection, 10 mg/mL

Read this carefully before you start taking NUBAIN and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about NUBAIN.

Serious Warnings and Precautions

- **NUBAIN will be given to you by a health professional who is specially trained to give this kind of drug.**
- **Even if you take NUBAIN as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your prescriber (e.g., doctor).**
- **You may get life-threatening breathing problems while taking NUBAIN. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **If a person has not been prescribed NUBAIN, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took NUBAIN while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
  - **has changes in their breathing (such as weak, difficult or fast breathing)**
  - **is unusually difficult to comfort**
  - **has tremors (shakiness)**
  - **has increased stools, sneezing, yawning, vomiting, or fever**

  Seek immediate medical help for your baby.
- **Taking NUBAIN with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**

What is NUBAIN used for:

NUBAIN is indicated in adults:

- for the relief of moderate to severe pain.
- to aid anesthesia for surgery.
- to help manage pain before and after surgery.
- to help manage pain during child birth.

What does NUBAIN work:

NUBAIN is a pain medication belonging to the class of medicines known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

NUBAIN is used to treat severe pain in patients who need an opioid administered by injection. This is given under the skin, into the muscle or vein in doses or concentrations that are higher than those usually needed

What are the ingredients in NUBAIN:

Medicinal ingredients: Nalbuphine hydrochloride
Non-medicinal ingredients: Sodium chloride, sodium citrate dihydrate, citric acid and water for injection. pH adjusted with hydrochloric acid.

NUBAIN comes in the following dosage forms:

Solution for injection: 10 mg/mL.

Do not use NUBAIN if:

- your doctor did not prescribe it for you
- you are allergic to nalbuphine hydrochloride or any of the other ingredients in NUBAIN
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are pregnant or planning to become pregnant or you are in labour
- you are breastfeeding
- are less than 18 years of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NUBAIN. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver or lung disease
- have heart disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have problems with your thyroid, adrenal or prostate gland
- have, or had in the past hallucinations or other severe mental problems
- are breastfeeding
- suffer from migraines
- are planning to become pregnant

Other warnings you should know about:
Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

Pregnancy, nursing, labour and delivery:
Do not use NUBAIN while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. NUBAIN can then cause life-threatening breathing problems in your unborn baby or nursing infant. Your doctor will determine if the benefits of using NUBAIN outweigh the risks to your unborn baby or nursing infant.

If you are pregnant and are taking NUBAIN, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your doctor will monitor and guide you on how to slowly stop taking NUBAIN. This may help avoid serious harm to your unborn baby.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:
- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off NUBAIN.

Serotonin Syndrome: NUBAIN can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive

system work. You may develop Serotonin Syndrome if you take NUBAIN with certain anti-depressants or migraine medications.

Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Sexual Function/Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to NUBAIN. NUBAIN can cause:

- drowsiness
- dizziness or
- lightheadedness

This can usually occur after you take your first dose and when your dose is increased.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NUBAIN:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. Do not drink alcohol while you are taking NUBAIN. It can lead to:
  - drowsiness
  - unusually slow or weak breathing
  - serious side effects or
  - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by NUBAIN
- other opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). Do not take NUBAIN with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- warfarin (such as coumadin) and other anticoagulants (used for prevention or treatment of blood clots)
- anti-retroviral drugs (used to treat viral infections)
- anti-fungal drugs (used to treat fungal infections)

- antibiotic drugs (used to treat bacterial infections)
- some heart medication (such as beta blockers)
- drugs used to treat migraines (e.g. triptans)
- grapefruit juice
- St. John's Wort

How to take NUBAIN:
NUBAIN will be given to you as an injection either under the skin, into a muscle or into your vein.
Your doctor will determine your dose based on how much you weigh.

Your dose is tailored/personalized just for you. Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take NUBAIN for up to 7 days. If you need to take NUBAIN for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your doctor to determine if you still need NUBAIN.

If your pain increases or you develop any side effect as a result of taking NUBAIN, tell your doctor immediately.

Stopping your Medication

If you have been taking NUBAIN for more than a few days, you should not stop taking it all of a sudden. You should check with your doctor for directions on how to slowly stop taking it. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness
- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking NUBAIN.

Overdose:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs of overdose may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

Missed Dose:
If a dose has been missed, tell your doctor or health professional as soon as possible. The next dose should be given to you at the next scheduled time and in the normal amount.

What are the possible side effects from being given NUBAIN?

These are not all the possible side effects you may feel when taking NUBAIN. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using NUBAIN.

Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
RARE	**Skin: reactions at the injection site such as pain, swelling, redness, burning and hot sensations, itching, rash.**	☐		
	Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin.			√
	Respiratory Depression: slow, shallow or weak breathing.			√
	Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
	Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			√
	Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		√	
	Fast, Slow or Irregular Heartbeat: heart palpitations.		√	
	Low Blood Pressure: dizziness, fainting, light-headedness.	√		
	Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone.
3 ways to report:

- Online at MedEffect: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html).

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep unused or expired NUBAIN in a secure place to prevent theft, misuse or accidental exposure
- NUBAIN should be stored between 15°C and 30°C and protected from light. Store in carton until contents have been used.
- Keep NUBAIN under lock, out of sight and reach of children.
- Never take medicine in front of small children as they will want to copy you. Accidental exposure by a child is dangerous and may result in death. If a child accidentally takes NUBAIN, get emergency help right away.

If you want more information about NUBAIN:

- Talk to your healthcare professional
- Find the full prescribing information that is prepared for healthcare professionals and includes this consumer medication information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.sandoz.com, or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

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