# Nalbusol Injection
(Nalbuphine HCl)

# نیلبوسول انجیکشن
(نیلبوفن ہائیڈروکلورائیڈ)

**COMPOSITION**

**Nalbusol Injection 10mg/ml**

Each ml contains:

Nalbuphine hydrochloride .....10mg

**(Innovator's specifications)**

**Nalbusol Injection 20mg/ml**

Each ml contains:

Nalbuphine hydrochloride .....20mg

**(Innovator's specifications)**

**DESCRIPTION**

NALBUSOL (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. It appears to be an agonist at kappa opioid receptors and an antagonist or partial agonist at mu opioid receptors.

**MECHANISM OF ACTION**

Nalbuphine is an agonist at kappa opioid receptors and an antagonist at mu opioid receptors.

**INDICATIONS**

NALBUSOL is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. NALBUSOL 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, reserve NALBUSOL for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]

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

**DOSAGE & ADMINISTRATION**

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

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

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

Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with NALBUSOL and adjust the dosage accordingly.

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. In nontolerant individuals, the recommended single maximum dose is 20 mg with a maximum total daily dose of 160 mg. The use of NALBUSOL 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 NALBUSOL may be followed by respiratory depression which can be reversed with the opioid antagonist naloxone hydrochloride.

**Titration and Maintenance of Therapy**

Individually titrate NALBUSOL to a dose that provides adequate analgesia and minimizes adverse reactions. Continually re-evaluate 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. 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 NALBUSOL**

When a patient who has been taking NALBUSOL regularly and may be physically dependent no longer requires therapy with NALBUSOL, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue NALBUSOL in a physically-dependent patient.

**PHARMACOKINETICS**

The onset of action of NALBUSOL 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 metabolic pathway for nalbuphine has not been defined, but is likely hepatic.

**WARNINGS**

**Life-Threatening Respiratory Depression**

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO) 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 NALBUSOL, 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 NALBUSOL.

**Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants**

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

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

The use of NALBUSOL in patients with acute or severe bronchial asthma in an un-monitored setting or in the absence of resuscitative equipment is contraindicated.

**Patients with Chronic *Pulmonary Disease:***

NALBUSOL-treated patients with significant chronic obstructive pulmonary disease 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 NALBUSOL.

***Elderly, Cachectic, or Debilitated Patients:*** Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier Patients Monitor such patients closely, particularly when initiating and titrating NALBUSOL and when NALBUSOL is given concomitantly with other drugs that depress respiration. 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.

**Severe Hypotension**

NALBUSOL may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of NALBUSOL. In patients with circulatory shock, NALBUSOL may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of NALBUSOL in patients with circulatory shock.

**Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness**

In patients who may be susceptible to the intracranial effects of $CO_2$ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), NALBUSOL may reduce respiratory drive, and the resultant $CO_2$ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with NALBUSOL. Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of NALBUSOL in patients with impaired consciousness or coma.

**Risks of Use in Patients with Gastrointestinal Conditions**

NALBUSOL is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. Nalbuphine may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

**Increased Risk of Seizures in Patients with Seizure Disorders**

The nalbuphine in NALBUSOL may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during NALBUSOL therapy.

**Withdrawal**

The use of NALBUSOL, a mixed agonist/antagonist opioid analgesic, in patients who are receiving a full opioid agonist analgesic may reduce the analgesic effect and/or precipitate withdrawal symptoms. Avoid concomitant use of NALBUSOL with a full opioid agonist analgesic. When discontinuing NALBUSOL in a physically-dependent patient, gradually taper the dosage. Do not abruptly discontinue NALBUSOL in these patients.

**Risks of Driving and Operating Machinery**

NALBUSOL may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of NALBUSOL and know how they will react to the medication. Maintain patient under observation until recovered from NALBUSOL effects that would affect driving or other potentially dangerous tasks.

**Use in Pregnancy (Other Than Labor)**

Severe fetal bradycardia has been reported when NALBUSOL is administered during labor. Naloxone may reverse these effects. Although there are no reports of fetal bradycardia earlier in pregnancy, it is possible that this may occur. Avoid the use of NALBUSOL in pregnant women unless the potential benefit outweighs the risk to the fetus, and if appropriate measures such as fetal monitoring are taken to detect and manage any potential adverse effect on the fetus.

**Use during Labor and Delivery**

The placental transfer of nalbuphine is high, rapid, and variable with a maternal to fetal ratio ranging from 1:0.37 to 1:6. Fetal and neonatal adverse effects that have been reported following the administration of nalbuphine to the mother during labor include fetal bradycardia, respiratory depression at birth, apnea, cyanosis, and hypotonia. Some of these events have been life-threatening. Maternal administration of naloxone during labor has normalized these effects in some cases. Severe and prolonged fetal bradycardia has been reported. Permanent neurological damage

attributed to fetal bradycardia has occurred. A sinusoidal fetal heart rate pattern associated with the use of nalbuphine has also been reported. NALBUSOL 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 NALBUSOL has been used.

**Addiction, Abuse, and Misuse**

Nalbuphine hydrochloride is a synthetic opioid agonist-antagonist analgesic. As an opioid, NALBUSOL exposes users to the risks of addiction, abuse, and misuse. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed NALBUSOL. Addiction can occur at recommended dosages and if the drug is misused or abused. Assess each patient's risk for opioid addiction, abuse, or misuse. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing NALBUSOL. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

**PRECAUTIONS**

***General***

**Impaired Renal or Hepatic Function**

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

**Myocardial Infarction**

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

**Cardiovascular System**

During evaluation in anesthesia, a higher incidence of bradycardia has been reported in patients who did not receive atropine pre-operatively.

**Laboratory Tests**

NALBUSOL 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.

***Information for Patients***

Patients should be advised of the following information:

**Serotonin Syndrome**

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

**Monoamine Oxidase Inhibitor (MAOI) Interaction**

Inform patients to avoid taking while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking NALBUSOL.

**Constipation**

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

**DRUG INTERACTIONS**

**Benzodiazepines and other Central Nervous System (CNS) Depressants**

Although NALBUSOL possesses opioid antagonist activity, there is evidence that in nondependent patients it will not antagonize an opioid analgesic administered just before, concurrently, or just after an injection of NALBUSOL. Therefore, due to additive pharmacologic effects, the concomitant use of other opioid analgesics, benzodiazepines or other CNS depressants such as alcohol, other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, can increase the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation.

**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.

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

**Muscle Relaxants**

Nalbuphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

**Diuretics**

Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

**Anticholinergic Drugs**

The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

Monitor patients for signs of urinary retention or reduced gastric motility when NALBUSOL is used concomitantly with anticholinergic drugs.

**Monoamine Oxidase Inhibitors (MAOIs)**

MAOI (e.g., phenelzine, tranylcypromine, linezolid) interactions with opioids may manifest as serotonin syndrome or opioid toxicity.

The use of NALBUSOL is not recommended for patients taking MAOIs or within 14 days of stopping such treatment. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.

**SIDE EFFECTS:**

**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.

**Post-marketing Experience**

The following adverse reactions have been identified during post approval use of nalbuphine.

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 NALBUSOL treatment. Fetal death has been reported where mothers received NALBUSOL during labor and delivery.

**CONTRAINDICATIONS**

NALBUSOL is contraindicated in patients with:

- Significant respiratory depression.
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment.
- Known or suspected gastrointestinal obstruction, including paralytic ileus.
- Hypersensitivity to nalbuphine to any of the other ingredients in NALBUSOL.

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

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

**STORAGE & INSTRUCTIONS:**

Store between 15-25°C in a cool and dry place.
Protect from heat and sunlight.
Keep away from the reach of the children.
Do not use the injection if any particulate matter is present, container is leaking or solution is cloudy.

**To be sold on the prescription of a registered medical practitioner only.**

**For Intravenous, Intramuscular and Subcutaneous use only.**

**HOW SUPPLIED**

**Nalbusol Injection 10mg/ml**
1ml x10 ampoules.
**Nalbusol Injection 20mg/ml**
1ml x 10 ampoules.

## خوراک وطریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

## ہدایات:

دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان ٹھنڈی اور خشک جگہ پر رکھیں۔ دھوپ اور گرمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔ انجیکشن کے لیک ہونے، دھندلا ہونے یا اس میں ذرات نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔ صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔ صرف وریدی، عضلاتی اور جلد کے نیچے استعمال کیلئے ہے۔

Manufactured by:
**PHARMASOL PRIVATE LIMITED**
Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.