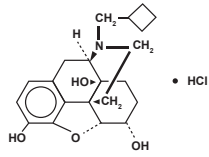
Nubiget™
(Nalbuphine HCl)

نیوبیگیٹ

Injection
10mg/mL, 20mg/mL

DESCRIPTION
Nubiget (Nalbuphine HCl) is a synthetic opioid agonist-antagonist analgesic of the phenanthrene series. It is chemically related to both the widely used opioid antagonist, naloxone, and the potent opioid analgesic, oxymorphone. Chemically Nalbuphine HCl is 17-(cyclobutylmethyl)-4,5α-epoxymorphinan-3,6α,14-triol hydrochloride. Its molecular formula is $C_{21}H_{27}NO_4 \cdot HCl$ and structural formula is:



Nalbuphine HCl

QUALITATIVE AND QUANTITATIVE COMPOSITION
Nubiget (Nalbuphine HCl) Injection is available for administration as:

Nubiget Injection 10mg/mL
Each 1mL ampoule contains:
Nalbuphine HCl….10mg

Nubiget Injection 20mg/mL
Each 1mL ampoule contains:
Nalbuphine HCl….20mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Nalbuphine HCl is an agonist at kappa opioid receptors and an antagonist at mμ opioid receptors.

Pharmacokinetics
The onset of action of Nalbuphine HCl 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 HCl is 5 hours, and in clinical studies the duration of analgesic activity has been reported to range from 3 to 6 hours.

THERAPEUTIC INDICATIONS
Nubiget (Nalbuphine HCl) Injection is indicated for the relief of moderate to severe pain. Nubiget (Nalbuphine HCl) Injection can also be used as a supplement to balanced anesthesia, an adjunct to preoperative and postoperative analgesia, and obstetrical analgesia during labor and delivery.

DOSAGE & ADMINISTRATION
Important Dosage and Administration Instructions
Nubiget (Nalbuphine HCl) Injection should be administered as a supplement to general anesthesia only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

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

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

Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with Nubiget (Nalbuphine HCl) Injection 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 Dosing
The usual recommended adult dose is 10mg 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 20mg with a maximum total daily dose of 160mg.

Balance Anaesthesia
The use of Nubiget (Nalbuphine HCl) Injection as a supplement to balanced anesthesia requires larger doses than those recommended for analgesia. Induction doses of Nubiget (Nalbuphine HCl) Injection 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 Nubiget (Nalbuphine HCl) Injection may be followed by respiratory depression which can be reversed with the opioid antagonist naloxone hydrochloride.

Titration and Maintenance of Therapy
Individually titrate Nubiget (Nalbuphine HCl) Injection to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving Nubiget (Nalbuphine HCl) Injection 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.

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

Special Population
Hepatic Impairment
Patients with liver dysfunction may show an exaggerated response to customary doses. In these individuals, Nubiget (Nalbuphine HCl) Injection should be used with caution and administered in reduced amounts.

Renal Impairment
Patients with renal dysfunction may show an exaggerated response to customary doses. In these individuals, Nubiget (Nalbuphine HCl) Injection should be used with caution and administered in reduced amounts.

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

Pediatrics
Use of Nubiget (Nalbuphine HCl) Injection is not recommended in patients under 18 years of age.

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. Nubiget (Nalbuphine HCl) Injection should be initiated at a low dose and slowly titrated to effect.

Incompatibility With Other Therapeutic Agents
Nubiget (Nalbuphine HCl) Injection is physically incompatible with nafcillin and ketorolac. Solutions of these drugs should not be mixed.

ADVERSE REACTIONS
Common
Sedation, nausea, vomiting and constipation.

Less common
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.
Cardiovascular: Hypertension, hypotension, bradycardia and tachycardia.
Gastrointestinal: Cramps, dyspepsia and bitter taste.
Respiration: Depression, dyspnea and asthma.
Dermatological: Itching, burning and urticaria.
Miscellaneous: Speech difficulty, urinary urgency, blurred vision, flushing and warmth.
Allergic Reactions: Shock, respiratory distress, respiratory arrest, bradycardia, cardiac arrest, hypotension, or laryngeal edemastridor, bronchospasm, wheezing, edema, rash, pruritis, nausea, vomiting, diaphoresis, weakness, and shakiness.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Nalbuphine HCl is contraindicated in:
- Patients who are hypersensitive to the active substance Nalbuphine HCl or other opioid analgesics or to any excipient of the product.
- 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.

PRECAUTIONS

WARNINGS

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, Nalbuphine HCl 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.

Addiction, Abuse, and Misuse
Nalbuphine HCl 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 Nalbuphine HCl, and all patients should be monitored regularly for the development of these behaviours or conditions. Nalbuphine HCl should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Nalbuphine HCl. 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 Nalbuphine HCl 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 Nalbuphine HCl, especially by children, can result in a fatal overdose of Nalbuphine HCl.

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of Nalbuphine HCl during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening.

Interaction with Alcohol
The co-ingestion of alcohol with Nalbuphine HCl should be avoided as it may result in dangerous additive effects, causing serious injury or death.

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.
- Reserve concomitant prescribing of Nalbuphine HCl 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 Nalbuphine HCl to anyone other than for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. Nalbuphine HCl should be stored securely to avoid theft or misuse.
- Patients should be cautioned not to consume alcohol while taking Nalbuphine HCl 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 HCl can occur at particularly high doses. A Nalbuphine HCl dose reduction or change in opioid may be required.

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

Cardiovascular
Nalbuphine HCl 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 Nalbuphine HCl. The use of Nalbuphine HCl 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.

Myocardial Infarction
As with all potent analgesics, Nalbuphine HCl 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 Nalbuphine HCl 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 Nalbuphine HCl and there is a potential for development of psychological dependence. Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control.

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

Gastrointestinal Effects
Nalbuphine HCl 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.

Biliary Tract Surgery
Nalbuphine HCl 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.

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 Nalbuphine HCl for at least 24 hours before the operation and Nalbuphine HCl should not be used in the immediate post-operative period.
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
Nalbuphine HCl 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 HCl with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

Impaired Renal or Hepatic Function
Because Nalbuphine HCl 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, Nalbuphine HCl should be used with caution and administered in reduced amounts.

Use in Drug and Alcohol Addiction
Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to Nalbuphine HCl; extreme caution and awareness is warranted to mitigate the risk.

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.

Pregnancy
Nalbuphine HCl crosses the placental barrier and is contraindicated in pregnant women.

Nursing Mothers
Since opioids can cross the placental barrier and are excreted in breast milk, Nalbuphine HCl 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.

DRUG INTERACTIONS
Central Nervous System (CNS) Depressants
Both magnitude and duration of CNS and cardiovascular effects may be enhanced when Nalbuphine HCl is administered to patients receiving barbiturates, benzodiazepines, neuroleptics, halogenic gases and other nonselective CNS depressants (e.g. alcohol). When patients have received such drugs, the dose of Nalbuphine HCl required will be less than usual. Likewise, following the administration of Nalbuphine HCl 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
Co-administration of Nalbuphine HCl 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.

Muscle Relaxants
Nalbuphine HCl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Nalbuphine HCl Injection and/or the muscle relaxant as necessary.

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

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

Drug-Lifestyle Interactions
The concomitant use of alcohol should be avoided.

Monitoring and Laboratory Tests
Nalbuphine HCl may interfere with enzymatic methods for the detection of opioids depending on the specificity and sensitivity of the laboratory tests.

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

Treatment
In case of overdose, priorities are the re-establishment of a patent and protected air way 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 HCl overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to Nalbuphine HCl Injection overdose.
Because the duration of opioid reversal is expected to be less than the duration of action of Nalbuphine HCl, 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
Do not store above 30°C.
Protect from excessive light and heat.
Store in carton until contents have been used.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Nubiget (Nalbuphine HCl) Injection 10mg/mL is available in pack of 1mL x 5 ampoules.
Nubiget (Nalbuphine HCl) Injection 20mg/mL is available in pack of 1mL x 5 ampoules.

Keep out of reach of children.

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

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Getz pharma (PVT) LIMITED
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