For Medical Professional only

Bunail®
INJECTION

(Nalbuphine HCl)

بونیل انجکشن
(نیلبوفین ہائیڈروکلورائیڈ)

DESCRIPTION:
BUNAIL (nalbuphine hydrochloride) is a synthetic opioid agonist-antagonist analgesic of the phenanthrene series. It is chemically related to both the widely used opioid antagonist, naloxone, and the potent opioid analgesic, oxymorphone. Chemically nalbuphine hydrochloride is 17-(cyclobutylmethyl)¬ 4,5α-epoxymorphinan-3,6α,14-triol hydrochloride. Nalbuphine hydrochloride molecular weight is 393.91 and is soluble in H2O (35.5 mg/mL at 25ºC) and ethanol (0.8%); insoluble in CHCl3 and ether. The molecular formula is $C_{21}H_{27}NO_4$ • HCl.

COMPOSITION:
Bunail 10mg injection: Each ml contains: Nalbuphine HCl M.S. …. 10 mg
(Product Specs.: Bosch)

Bunail 20mg injection: Each ml contains: Nalbuphine HCl M.S. …. 20 mg
(Product Specs.: Bosch)

CLINICAL PHARMACOLOGY:
Pharmacodynamic Properties:
Pharmacotherapeutic group: opioid agonist-antagonists. ATC code: N02AF02.

Mechanism of Action:
Nalbuphine is an agonist at kappa opioid receptors and an antagonist at mu opioid receptors. BUNAIL is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis up to a dosage of approximately 30 mg. The opioid antagonist activity of BUNAIL is one-fourth as potent as nalorphine and 10 times that of pentazocine. BUNAIL may produce the same degree of respiratory depression as equianalgesic doses of morphine. BUNAIL exhibits a ceiling effect such that increases in dose greater than 30 mg do not produce further respiratory depression in the absence of other CNS active medications affecting respiration.

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

Pharmacokinetic Properties
The onset of action of BUNAIL 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.

THERAPEUTIC INDICATIONS:
BUNAIL is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. BUNAIL can also be used as a supplement to balanced anesthesia, for preoperative and postoperative analgesia, and for obstetrical analgesia during labor and delivery.

DOSAGE AND ADMINISTRATION:
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 BUNAIL and adjust the dosage accordingly.

Children	0.3mg/kg may be given initially, repeated once or twice as necessary.
Adult	The usual recommended adult dose is 10mg for a 70kg 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 non-tolerant individuals, the recommended single maximum dose is 20mg, with a maximum total daily dose of 160mg.
Balanced Anesthesia	The use of Bunail as a supplement to balanced anesthesia requires larger doses than those recommended for analgesia. Induction doses of Bunail range from 0.3mg/kg to 3mg/kg intravenously to be administered over a 10 to 15 minute period with maintenance doses of 0.25 to 0.5mg/kg in single intravenous administrations as required. The use of Bunail injection may be followed by respiratory depression which can be reversed with the opioid antagonist (naloxone hydrochloride).

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

Elderly:
Elderly patients (aged 65 years or older) may have increased sensitivity to BUNAIL. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate

the dosage of BUNAIL slowly in geriatric patients.

Patients with Renal Impairment:

Nalbuphine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Method of Administration:

BUNAIL 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.

BUNAIL is a sterile solution suitable for subcutaneous, intramuscular, or intravenous injection. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

CONTRAINDICATIONS:

BUNAIL 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 BUNAIL.

WARNINGS AND PRECAUTIONS:

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. 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 BUNAIL.

Overestimating the BUNAIL dosage when converting patients from another opioid product can result in a fatal overdose with the first dose. Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper.

Patients with Chronic Pulmonary Disease

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

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 BUNAIL and when BUNAIL 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. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency.

Severe Hypotension

BUNAIL 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. Monitor these patients for signs of hypotension after initiating or titrating the dosage of BUNAIL. In patients with circulatory shock, BUNAIL may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of BUNAIL in patients with circulatory shock.

Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness.

In patients who may be susceptible to the intracranial effects of CO2 retention, BUNAIL may reduce respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with BUNAIL. Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of BUNAIL in patients with impaired consciousness or coma.

Patients with Gastrointestinal Conditions

BUNAIL is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The nalbuphine in BUNAIL 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.

Patients with Seizure Disorders

The nalbuphine in BUNAIL 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 BUNAIL therapy.

Withdrawal

The use of BUNAIL, 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 BUNAIL with a full opioid agonist analgesic. When discontinuing BUNAIL in a physically-dependent patient, gradually taper the dosage, gradually by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. Do not abruptly discontinue BUNAIL in these patients.

Impaired Renal or Hepatic Function

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

Myocardial Infarction

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

Cardiovascular System

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

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon. 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.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Constipation

Advise patients of the potential for severe constipation, including management

instructions and when to seek medical attention.

DRUG INTERACTIONS:

Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of BUNAIL with benzodiazepines or other CNS depressants. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. . 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. 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.

Concomitant use with 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), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue), has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue BUNAIL 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. Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of BUNAIL and/or the muscle relaxant as necessary.

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 BUNAIL 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 (e.g., respiratory depression, coma). The use of BUNAIL 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.

ADVERSE EFFECTS:

Most frequent adverse reaction with BUNAIL was sedation (36%).
Less frequent reactions were: sweaty/clammy (9%), nausea/vomiting (6%), dizziness/vertigo (5%), dry mouth (4%), and headache (3%).
Other adverse reactions which occurred (reported incidence of 1% or less) were:
CNS Effects: Nervousness, depression, restlessness, crying, euphoria, floating, hostility, unusual dreams, confusion, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality.
Cardiovascular :Hypertension, hypotension, bradycardia, tachycardia.
Gastrointestinal: Cramps, dyspepsia, bitter taste.
Respiratory Depression: dyspnea, asthma.
Dermatologic: Itching, burning, urticarial.
Miscellaneous: Speech difficulty, urinary urgency, blurred vision, flushing and warmth.
Allergic Reactions: Anaphylactic/anaphylactoid and other serious hypersensitivity reactions and may required immidiate supportive medical treatment

USE IN PREGNANCY AND LACTATION:

Pregnancy:

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Severe fetal bradycardia has been reported when BUNAIL is administered during labor. Naloxone may reverse these effects. Although there are no reports of fetal bradycardia earlier in pregnancy. Avoid the use of BUNAIL 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. Newborns should be monitored for respiratory depression, apnea, bradycardia and arrhythmias if BUNAIL has been used.

Lactation:

BUNAIL (nalbuphine hydrochloride) is excreted in maternal milk but only in a small amount (less than 1% of the administered dose) and with a clinically insignificant effect. Infants exposed to BUNAIL through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

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 BUNAIL 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.

STORAGE AND INSTRUCTIONS:

Protect from heat & sunlight, store at or below 25°C. Avoid freezing.
The expiration date refer to the product correctly stored at the required condition. Keep out of the reach of children.
Precautions: Do not use if injection is leaking, solution is cloudy or contains undissolved particles.
Patients and healthcare professionals can also report suspected adverse drug reaction at ade@bosch-pharma.com.
To be sold on prescription of a registered medical practitioner only.

PRESENTATION:

Bunail injection 10mg: Pack of 5 x 1ml Ampoules
Bunail injection 20mg: Pack of 5 x 1ml Ampoules

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات:- دھوپ اور گرمی سے محفوظ ۲۵ ڈگری سینٹی گریڈ یا اس سے کم درجہ حرارت پر رکھیں۔
منجمد ہونے سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
احتیاط: انجکشن لیک ہونے، دھندلا ہونے یا اس میں کوئی غیر حل پذیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔
صرف مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔

Manufactured by:
Bosch Pharmaceuticals (Pvt) Ltd.
221-223, Sector 23, Korangi Industrial Area,
Karachi - Pakistan

ISO 9001:2015 Certified Company