# MORPHEAS INJECTION 10 MG/ ML

**DESCRIPTION:**

**MORPHEAS INJECTION 10 MG/ ML:** A colourless solution to a light pale yellow solution.

**COMPOSITION:**
Each ml contains Morphine Sulphate BP 10 mg/ml. [Preservative free]

**PHARMACODYNAMICS:**
Morphine is an opioid analgesic. It acts mainly on the central nervous system and smooth muscle. Although morphine is predominantly a central nervous system depressant it has some central stimulant actions which result in nausea and vomiting and miosis. Morphine generally increases smooth muscle tone, especially the sphincters of the gastrointestinal tract. Morphine and related analgesics may produce both physical and psychological dependence and should therefore be used with discrimination. Tolerance may also develop.

**PHARMACOKINETICS:**
Morphine salts are absorbed from the gastrointestinal tract but their effects by this route are not entirely predictable; after subcutaneous or intramuscular injection morphine is readily absorbed into the blood. It undergoes significant first-pass metabolism in the liver. Morphine is distributed throughout the body but mainly in the kidneys, liver, lungs, and spleen, with lower concentrations in the brain muscle. Morphine diffuses across the placenta and traces also appear in milk and sweat. About 35% is protein bound.
Conjugation to morphine 3- and 6-glucuronides occur in the liver. About 10% of a dose of morphine is excreted through the bile into the faeces and the remainder is excreted in the urine, mainly as conjugates. About 90% of total morphine is excreted in 24 hours with traces up to 48 hours.

**INDICATIONS:**
Morphine sulphate via the intramuscular or subcutaneous route is indicated for the relief of moderate to severe pain not responsive to non-narcotic analgesics. It may also be used as pre-operative medication and as an analgesic adjunct in general anaesthesia.

**RECOMMENDED DOSAGE:**
**Dosage and Administration:** Morphine sulphate injection is intended for intramuscular, subcutaneous or intravenous injection. (This preparation is preservative free and may be administered intrathecally or epidurally).
**Adults:** The usual dosage for adults by i.m. or s.c. injection is 5 to 20 mg every 4 hours, intravenously, 2.5 to 15mg should be given by slow injection. This dose should be reduced in elderly patients, those with respiratory impairment and in patients receiving CNS depressants. In severe or chronic pain, the dose may need to be adjusted according to the response and tolerance of the patient.
**Renal and Hepatic Dysfunction:** Dosage reduction may be necessary in patients with renal or hepatic impairment.
**Paediatric:** Dosage in children should be adjusted according to body weight, 0.1 – 0.2 mg /kg every 4 hours. No dose should exceed 15 mg.
**Paediatric dose:** Analgesic – subcutaneous, 100 mg to 200 mg (0.1 to 0.2 mg) per kg of body weight every four hours as needed, not to exceed 15 mg per dose. Intravenous, 50 to 100 mcg (0.05 mg to 0.1 mg) per kg of body weight, administered very slowly.
**Preoperative** – Intramuscular, 50 to 100 mcg (0.05 to 0.1 mg) per kg of body weight, not to exceed 10 mg per dose.

**ROUTE OF ADMINISTRATION:** For i.m., i.v., s.c., intrathecal and epidural injection

**CONTRAINDICATIONS:**
Morphine Sulphate is contraindicated in patients hypersensitive to narcotics; following biliary tract surgery or surgical anastomosis; in patients who are taking or have taken MAO inhibitors within the previous fourteen days.
Morphine is generally contra-indicated in respiratory depression, acute bronchial asthma, heart failure secondary to chronic pulmonary disease, acute alcoholism, head injuries, raised intracranial pressure and convulsive states such as status epilepticus, tetanus or strychnine poisoning.

**WARNING AND PRECAUTIONS:**
1. Morphine should be used only when necessary with extreme caution in biliary surgery and acute pancreatitis (where bile duct surgical exploration is being undertaken, naloxone should be administered first).
2. The risk of morphine associated, or anaesthetic induced aspiration is enhanced by the reduction in gastric emptying caused by morphine.
3. Abrupt withdrawal of morphine in patients who are physically dependent on it may precipitate withdrawal syndrome, including convulsions. Continued administration of morphine may produce dependence.
4. The use of morphine in patients with chronic ulcerative colitis may stimulate motility in the colon. Toxic dilation may occur in patients with acute ulcerative colitis.
5. Morphine should be administered with extreme caution in aged or debilitated patients. Patients with reduced circulation volume, impaired myocardial function or who are taking sympatholytic drugs should be carefully observed for orthostatic hypotension.
6. Morphine should be given with caution to those with hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy and urethral stricture.
7. Respiratory depression: Therapeutic doses of narcotics may decrease respiratory drive and increase airway resistance to the point of apnoea in patients with acute asthma, chronic obstructive pulmonary disease or cor pulmonale, or those with a substantially decreased pulmonary reserve or respiratory depression. Resuscitative equipment and narcotic antagonists must be readily available.
8. Hepatic and renal impairment: Caution should be taken, in prescribing morphine for patients with severely impaired hepatic or renal function.

**Paediatric use:** Safety and effect in neonates have not been established.
**Warnings:** Narcotics analgesics have abuse potential. Psychological and physical dependence may occur with repeated dosing. Except in patients with terminal conditions, morphine should be restricted to short-term administration for the relief of severe pain not responding to non-narcotic analgesics.
Abrupt withdrawal of morphine in those physically dependent may precipitate withdrawal syndrome, including convulsions.
Use with extreme caution in patients with head injury and increased intracranial pressure. Respiratory depressant effects and ability to increase cerebrospinal fluid pressure may be exaggerated, and the clinical course obscured.
Therapeutic doses of narcotics may decrease respiratory drive and increase airway resistance to the point of apnoea in patients with acute asthma, chronic obstructive pulmonary disease or cor pulmonale, or those with a substantially decreased pulmonary reserve or respiratory depression. Resuscitative equipment and narcotic antagonists must be readily available.
**Compatibility:** Morphine salts are sensitive to changes in pH. Morphine is liable to be precipitated out of solution in an alkaline environment.
**Dependence of the morphine type:** The opioid analgesics are liable to subject to abuse. Drug dependence of the morphine type is a state arising from repeated administration of morphine or a drug with morphine-like effects; it is characterized by an overwhelming need to continue taking the drug or one with similar properties, by a tendency to increase the dose owing to the development of tolerance and by psychological and physical dependence on the drug.
Abrupt withdrawal of opiates from persons physically dependent on them precipitates a withdrawal syndrome, the severity of which depends on the individual, the drug used, the size and frequency of the dose, and the duration of drug use. Withdrawal symptoms usually begin within a few hours, reach a peak within 36 to 72 hours, and then gradually subside.

Withdrawal symptoms develop more slowly with methadone. Symptoms include yawning, mydriasis, lachrymation, rhinorrhoea, sneezing, muscle tremor, weakness, sweating, irritability, disturbed sleep or insomnia, restlessness, anorexia, nausea, vomiting, loss of weight, diarrhoea, dehydration, leucocytosis, bone pain, abdominal and muscle cramps, increases in heart-rate, respiratory and blood pressure, rise in temperature, and gooseflesh and vasomotor disturbances.
Withdrawal symptoms may be terminated by a suitable dose of morphine or related drug.
Some physiological values may not return to normal for several months following the acute withdrawal syndrome.
Withdrawal therapy requires sustained surveillance and patients should be persuaded to enter hospital or be referred to a treatment center. Withdrawal may be affected slowly or rapidly. The usual method is to replace the drug of dependence with methadone.

Risks from Concomitant Use with Benzodiazepines:
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Morpheas Injection with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.
If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.
If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, 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 Morpheas Injection is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine 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 benzodiazepines (See Drug Interactions).
Serotonin Syndrome with Concomitant Use of Serotonergic Drugs:
Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of Morpheas Injection with serotonergic drugs (See Interactions with Other Medicaments). This may occur within the recommended dosage range.
Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g.hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g.nausea, vomiting, diarrhoea) and can be fatal (See Interactions with Other Medicaments). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue Morpheas Injection if serotonin syndrome is suspected.
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, decreased appetite, 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 dosing 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.
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 Postmarketing Experience).

**INTERACTIONS WITH OTHERS MEDICAMENTS:**
The depressant effects of morphine are potentiated by other CNS depressants such as alcohol, sedatives, antihistamine, neuroleptics (e.g. phenothiazines, butyrophenones) tricyclic antidepressants and general anaesthetics. The action of morphine on the gastrointestinal tract may influence absorption of other drugs.
Concurrent use with Metoclopramide may antagonize the effects of metoclopramide on gastrointestinal mobility. Used with Tincture of Opium or paregoric may increase the risk of severe constipation as well as CNS depression.
Concurrent use with anticholinergics like atropine, propantheline etc. may increase the risk of severe constipation, which may lead to paralytic ileus and/or urinary retention.
**Benzodiazepines**
Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.
The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at GABAA sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions).
Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.
**Serotonergic Drugs**
The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Morpheas Injection if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (See Warnings and Precautions).

**USE IN PREGNANCY AND LACTATION:**
**Use in pregnancy:** Narcotic analgesics may cause respiratory depression in the newborn infant. These products should only be used during labour after weighing the needs of the mother against the risk to the foetus. Morphine may prolong labour by reducing the strength and frequency of uterine contractions. Infants born of mothers who have been taking morphine chronically may exhibit withdrawal symptoms.
To be used with caution in premature infants or during labour for delivery of premature infants.
**Use in lactation:** Morphine appears in breast milk. While the concentrations in breast milk following usual therapeutic doses in the mother may not be clinically significant, morphine administration to nursing mothers is not recommended.

**SIDE EFFECTS/ ADVERSE EFFECTS:**
**Adverse Reactions:** Respiratory depression is the major hazard of morphine therapy, especially since toxic doses vary considerably between individuals.
**More common:** Light headedness, dizziness, sedation, nausea, vomiting, constipation and sweating. These effects seem to be more prominent in ambulatory patients and those not experiencing severe pain and may be relieved by reducing the dose slightly and lying the patient down.
**Other:**
**Central nervous system:** Euphoria, dysphoria, weakness, headache, delirium, insomnia, anxiety, agitation, tremor, drowsiness, uncoordinated muscle movements, transient hallucinations, disorientation, visual disturbance, miosis.
**Gastrointestinal:** Dry mouth, anorexia, biliary tract spasm.
**Genito-urinary:** Urinary retention, antidiuretic effect, reduced libido and/or potency.
**Cardiovascular:** Facial flushing, tachycardia, bradycardia, palpitations, faintness, syncope, orthostatic hypotension.
**Hypersensitivity:** Pruritus, urticaria and other skin rashes, oedema. These and other allergic reactions, eg. wheezing may be related to histamine release and may be seen more frequently in asthmatic patients.

**Miscellaneous:** Pain at injection site local tissue irritation and induration following s.c. administration.

**Post marketing Experience:**

Serotonin syndrome (See Warnings and Precautions)

Adrenal insufficiency (See Warnings and Precautions)

***Androgen deficiency:*** Cases of androgen deficiency have occurred with chronic use of opioids. 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.

***Infertility:*** Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

**SYMPTOMS AND TREATMENT OF OVERDOSE:**

**Symptoms:** Overdosage is characterized by respiratory depression with or without concomitant CNS depression. Also extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin and sometimes bradycardia and hypotension. In severe overdosage, apnoea, circulatory collapse, cardiac arrest and death may occur.

**Treatment:** Since respiratory arrest may result either through direct depression of the respiratory center or as the result of hypoxia, primary attention should be given to the establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The narcotic antagonist, naloxone is a specific antidote. Naloxone should be administered intravenously, simultaneously with respiratory resuscitation. As the duration of effect of naloxone may be considerably shorter than that of morphine, repeated administration may be necessary.

**INCOMPATIBILITIES:**

Compounds reported to be incompatible in solution with morphine salts include some barbiturates, pethidine, phenytoin, promethazine and thiopentone.

**STORAGE CONDITIONS:**

Store below 30ºC. Protect from light. KEEP OUT OF REACH OF CHILDREN. *JAUHKAN DARIPADA CAPAIAN KANAK-KANAK.*

**PACK SIZE:**

Pack in 10's ampoules of 1 ml / box.

**SHELF LIFE:**

Please refer to outer package.

**PRODUCT REGISTRATION HOLDER AND MANUFACTURER:**

**DUOPHARMA (M) SDN BHD**

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