

DBL™ Morphine Sulfate Injection BP

1. NAME OF THE MEDICINE

Morphine sulfate pentahydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of isotonic preparations of DBL Morphine Sulfate Injection BP contains morphine sulfate pentahydrate 5 mg, 10 mg, 15 mg or 30 mg. These are sterile solutions of morphine sulfate pentahydrate and sodium chloride in water for injections. 1N hydrochloric acid is used to adjust the pH. The pH of these solutions ranges from 3.2 to 4.0.

For the full list of excipients, see section **6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Solution for injection.

DBL Morphine Sulfate Injection BP is a clear colourless to slightly yellow, sterile solution. The solution does not contain any antioxidant or preservative.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Morphine sulfate pentahydrate is indicated for the relief of moderate to severe pain not responsive to non-opioid analgesics. It may also be used as a pre-operative medication and as an analgesic adjunct in general anaesthesia.

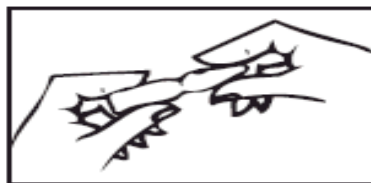
4.2 Dose and Method of Administration

NOTE: Opioid antagonists and facilities for administration of oxygen and control of respiration should be available during, and immediately following parenteral administration.

One Point Cut opening instructions



1. Locate the dot on the ampoule head.



2. Position thumbs on the head and body of the ampoule on the opposite side to the dot.



3. Opening away from the operator, apply quick even pressure with the thumbs to snap the ampoule neck.

Subcutaneous, intramuscular and slow intravenous administration

Adults: Morphine sulfate pentahydrate is usually administered by intramuscular or subcutaneous injection, in the range of 5 to 20 mg, depending on the cause of pain and the patient response. Doses may be repeated every 4 to 6 hours.

Morphine sulfate pentahydrate may also be given intravenously when a rapid onset of action is desired. The dose is usually in the range of 2.5 to 15 mg diluted in 4 to 5 mL of Water for Injections given slowly over 4 to 5 minutes.

Children: Morphine sulfate pentahydrate is given by intramuscular or subcutaneous injection in doses of 0.1 to 0.2 mg/kg bodyweight to a maximum of 15 mg. Injection may be repeated every 4 to 6 hours.

When a rapid onset of action is desirable, in a closely monitored environment, morphine may be titrated intravenously with caution, in a dose of 0.05 to 0.1 mg/kg, incrementally over 5 to 15 minutes. Repeat intravenous dosing is unsubstantiated as a method of analgesia in children.

Morphine sulfate pentahydrate is not usually given pre-operatively in children under 1 year, and it should be given with extreme care to neonates. It should not be given to premature infants (see section **4.3 Contraindications**).

Continuous intravenous infusion

The dosage of morphine should be titrated according to the patient's analgesic requirements and previous opiate experience. For the management of acute pain via intravenous infusion, most adults with no previous history of opioid intake can be continued on 0.5 to 2.0 mg/hr after adequate analgesia has been established.

In children, an infusion dose of 0.01 to 0.05 mg/kg/hr morphine to a maximum intravenous dose of 4 mg/hr is recommended.

It is recommended that an opioid antagonist and equipment for artificial ventilation be available.

Patient-controlled analgesia (PCA)

Patient-controlled analgesia allows patients to assess their own level of pain and consequently titrate the amount of morphine they require for adequate pain control against sedation and other side effects.

The dosages and time intervals are preset into a microprocessor-controlled infusion pump. When the patient experiences pain, a button is depressed by the patient and a dose of morphine is administered intravenously. If the patient should depress the button before the preset time interval (lockout interval) has elapsed, no extra drug is administered. For adults, demand doses of 0.5 to a maximum of 1.5 mg morphine have been given via PCA using a lockout interval of 6 to 10 minutes. Along with the self-administered dose of morphine, some syringe pumps also deliver a background continuous infusion of morphine at a basal rate. If a background infusion is adopted, a dose of 1 mg/hr morphine is often used in adults. Some

PCA pumps allow a maximum dosage over a defined period to be preset in order to avoid patient overdosage.

There is limited clinical experience of the use of patient-controlled analgesia in children. However, a demand dose of 0.01 to 0.025 mg/kg morphine has been used successfully in children and adolescents between the ages of 7 and 19 years with a lockout interval of 6 to 10 minutes. If a background infusion is employed, an infusion dose of 0.015 mg/kg/hr morphine may be used in children.

The demand dosage and lockout interval should be determined according to the patient's analgesic requirements. Patients receiving a background infusion of morphine should generally receive a smaller demand dose relative to equivalent patients utilising a demand dose only.

Techniques such as PCA with background continuous infusion are associated with a higher rate of adverse effects and require close monitoring.

General information for cancer pain

When morphine is administered by continuous intravenous or subcutaneous infusion for relief of severe, chronic pain associated with cancer, the dosage of morphine must be individualised according to the response and tolerance of the patient. In some patients with exceptionally severe, chronic pain it may be necessary to exceed the usual dosage. Reduced dosage is indicated in poor-risk patients, in very young or very old patients, and in patients receiving other CNS depressants.

Orally administered morphine should be used in preference to parenteral morphine whenever adequate pain control can be achieved by this route. However, oral morphine is often inadequate or impractical in the terminally ill patient.

Patients being converted from oral morphine to either intramuscular, intravenous or subcutaneous morphine require dosage reduction (about one-sixth), since about 60% of oral morphine is metabolised in first-pass metabolism (i.e. 1 mg of either intramuscular, subcutaneous or intravenous morphine for every 6 mg of oral morphine). The dose should then be titrated according to the patient's clinical response.

For cancer pain, DBL Morphine Sulfate Injection BP should be given regularly around the clock, in most instances every 4 hours. The basis of pain control with DBL Morphine Sulfate Injection BP should be regular scheduling rather than on an 'as required' or PRN narcotic order. Patients requiring high doses of morphine usually need to be awakened for medication during the night to prevent morning pain.

Morphine dosage increases

Dosage increases for intravenous, subcutaneous or intramuscular administration of morphine should not be made more frequently than every 24 hours, since it will take approximately 4 to 5 morphine half-lives to attain a new steady state concentration in a patient with normal liver and kidney function.

Following all dosage increases, the patient must be monitored closely for side effects, the most common being sedation, nausea, vomiting, constipation and hypotension.

Warning: As with all parenteral drug products, intravenous admixtures should be visually inspected for clarity, particulate matter, precipitate and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate or leakage should not be used. Development of a yellow colour in morphine solutions does not indicate toxicity or loss of potency or efficacy.

4.3 Contraindications

Morphine sulfate pentahydrate is contraindicated in the following situations:

- patients with known hypersensitivity to morphine or other opioids;
- with acute or severe bronchial asthma or other obstructive airways disease;
- respiratory insufficiency or depression, especially in the presence of cyanosis and/or excessive bronchial secretion;
- other conditions where respiratory reserve is depleted, such as severe emphysema, chronic bronchitis or kyphoscoliosis;
- cor pulmonale;
- severe CNS depression;
- diabetic acidosis where there is a danger of coma;
- severe liver disease or incipient hepatic encephalopathy;
- following biliary tract surgery or surgical anastomosis;
- biliary colic;
- gastrointestinal obstruction;
- suspected surgical abdomen;
- in patients who are taking or who have taken MAO inhibitors within the previous fourteen days;
- cardiac arrhythmias;
- heart failure secondary to pulmonary disease;
- acute alcoholism or delirium tremens;
- head injuries; brain tumour;
- raised intracranial or cerebrospinal pressure and in convulsive states such as status epilepticus, tetanus or strychnine poisoning (see section **4.4 Special Warnings and Precautions for Use**).

Morphine is contraindicated in premature infants or during labour for delivery of premature infants.

The administration of morphine via patient-controlled analgesia to children less than six years of age and adults with poor cognitive function is contraindicated.

The continuous intravenous infusion of morphine in patients with hepatic or renal disease is contraindicated (see section **4.4 Special Warnings and Precautions for Use**).

4.4 Special Warnings and Precautions for Use

Large doses and/or rapid administration of morphine may produce rapid onset of respiratory depression including central sleep apnoea (CSA) and sleep-related hypoxemia, bradycardia, or even cardiac arrest.

Morphine delays gastric emptying, which may be expected to increase the risks of aspiration, either associated with morphine induced CNS depression or coma, or during or after general anaesthesia.

Drug dependence and tolerance

Morphine can produce drug dependence and therefore has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration of morphine. However it should be noted that clinically significant respiratory depression, addiction, rapid tolerance and euphoria rarely develop when doses of morphine are carefully titrated against the pain in patients with terminal disease and severe pain.

Drug dependence does not develop if morphine is administered regularly at individually optimised doses to the cancer patient with moderate to severe pain. While a certain degree of physical dependence occurs, a psychological dependence does not occur. If a cancer patient no longer requires an opioid for pain control, a gradual reduction in dose will prevent any withdrawal symptoms, although these are usually mild or absent even after abrupt discontinuance. Clinically significant tolerance to morphine is unusual in the cancer patient being treated for severe pain. In most cases, a plateauing of dose requirements is seen, as a need to increase morphine dose means an increase in pain and not tolerance.

Withdrawal of morphine should be undertaken gradually, as abrupt withdrawal in patients who are physically dependent may precipitate an acute withdrawal syndrome, including convulsions.

Use with other CNS depressants

Morphine should be used with caution and in reduced dosage in patients who are concurrently receiving other opioid analgesics, general anaesthetics, phenothiazines, other tranquillisers, sedative hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension and profound sedation or coma may result.

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of morphine with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquillisers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as 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.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-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 section **4.5 Interactions with Other Medicines and Other Forms of 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 morphine 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 section **4.5 Interactions with Other Medicines and Other Forms of Interactions**). If respiratory depression of any form occurs, consider decreasing the opioid dosage using best practices for opioid taper.

Impaired respiration

The respiratory depressant effects of morphine and its capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse effects, including confusion, miosis and vomiting, which may obscure the clinical course of patients with head injuries. Morphine should only be used in such patients with extreme caution, and only if it is judged to be essential.

Respiratory depression is the chief hazard of all morphine preparations. Respiratory depression occurs most frequently in elderly and debilitated patients, and in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may significantly decrease pulmonary ventilation.

Morphine should be used with extreme caution in patients having an acute asthmatic attack, patients with chronic obstructive pulmonary disease or cor pulmonale, patients having a substantially decreased respiratory reserve, and patients with pre-existing respiratory depression, hypoxia or hypercapnia. In such patients, even the usual therapeutic doses of morphine may decrease respiratory drive while simultaneously increasing airways resistance to the point of apnoea (see section **4.3 Contraindications**).

Resuscitative equipment and opioid antagonist must be readily available.

Nervous system

The development of serotonin syndrome (SS), which is potentially life-threatening, has been reported with opioid use, including with morphine. These reports generally occurred when morphine was used concomitantly with serotonergic drugs (see section **4.5 Interactions with Other Medicines and Other Forms of Interactions**). Signs of SS may include clonus,

agitation, diaphoresis, tremor, hyperreflexia, hypertonia and temperature elevation.

Endocrine system

Cases of adrenal insufficiency have been reported with opioid use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure.

Hypotensive effect

The administration of morphine may result in severe hypotension in the post-operative patient or any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, shock, or the administration of such drugs as the phenothiazines or certain anaesthetics.

Morphine may produce orthostatic hypotension in ambulatory patients.

Supraventricular tachycardias

Because of possible vagolytic action that may produce a significant increase in the ventricular response rate, morphine should be used with caution in patients with atrial flutter and other supraventricular tachycardias.

Acute abdominal condition

The administration of morphine or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Morphine should be used with caution in patients with inflammatory or obstructive bowel disorders, or with ulcerative colitis, and should only be used when necessary in patients with acute pancreatitis.

Convulsions

Morphine may aggravate pre-existing convulsions in patients with convulsive disorders. If dosage is escalated substantially above recommended levels because of tolerance development, convulsions may occur in individuals without a history of convulsive disorders.

Other special risk patients

Morphine should be given with caution, and in reduced dosages, to certain patients, such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, myxoedema, and prostatic hypertrophy or urethral stricture. Caution should also be observed if morphine is administered to patients with toxic psychosis or myasthenia gravis. Morphine should be used with extreme caution in patients with disorders characterised by hypoxia, since even usual therapeutic doses of opioids may decrease respiratory drive to the point of apnoea while simultaneously increasing airway resistance.

Shock patients

In patients with shock, impaired perfusion may prevent complete absorption following

subcutaneous or intramuscular injection of morphine. Repeated administration may result in overdosage due to an excessive amount of morphine suddenly being absorbed when circulation is restored.

Use in renal or hepatic impairment

Morphine may have a prolonged duration and cumulative effect in patients with kidney or liver dysfunction. In these patients, analgesia may last for 6, 8 or even up to 24 hours following a standard dose. Continuous infusions are contraindicated in these patients (see section **4.3 Contraindications**).

Caution should be observed when morphine is administered to patients with impaired renal function, as the pharmacologically active metabolite, morphine-6-glucuronide, may accumulate in these patients. This may lead to CNS and respiratory depression.

Use in the elderly

Morphine should be administered with caution and in reduced dosages to elderly or debilitated patients. Respiratory depression occurs more frequently in these patients. The pharmacodynamics of morphine are more variable in geriatric patients than in younger adults. Therefore, initial dosage should be selected carefully based on clinical assessment of response to test doses and consideration of the patient's age and ability to clear the drug.

In older patients, the volume of distribution is considerably smaller and initial concentrations of morphine are correspondingly higher (see section **4.4 Special Warnings and Precautions for Use – Other special risk patients**).

Paediatric use

Safety and efficacy of morphine in neonates have not been established. However, neonates have an enhanced susceptibility to the respiratory depressant effects of morphine. Morphine should not be administered to premature infants (see section **4.3 Contraindications**).

Effects on laboratory tests

Morphine delays gastric emptying, thereby invalidating test results in gastric emptying studies.

Morphine may interfere with hepatobiliary imaging using technetium Tc^{99m} disofenin. Morphine may constrict the sphincter of Oddi and increase biliary tract pressure, preventing delivery of Tc^{99m} disofenin to the small bowel. These actions result in delayed visualisation, and thus resemble obstruction of the common bile duct.

4.5 Interactions with Other Medicines and Other Forms of Interactions

Morphine in combination with other opioid analgesics, phenothiazines, sedative hypnotics, and alcohol have additive depressant effects. Patients should be cautioned accordingly.

Acidifying agents generally increase the clearance of morphine, thus antagonising its effects, while alkalinising agents decrease clearance and so potentiate the effects of morphine.

CNS depressants: Morphine should be used with great caution and in reduced dosage in patients concurrently receiving other central nervous system depressants including other opioids, sedatives, hypnotics, general anaesthetics, phenothiazines, other tranquillisers and alcohol because of the risk of respiratory depression, hypotension and profound sedation or coma. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention	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 section 4.4 Special Warnings and Precautions for Use).
Examples	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquillisers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol.

Significant impairment of motor function has also been noted following concomitant morphine administration and alcohol ingestion.

Concurrent administration with tricyclic antidepressants or beta-blockers may enhance the CNS depressant effects of morphine.

Diazepam, when used following high doses of morphine, exacerbates the hypotensive effects produced by morphine, and is associated with reduced plasma catecholamine levels.

Antihypertensive agents: Concurrent administration of morphine may increase the hypotensive effects of antihypertensive agents or other drugs with hypotensive effects.

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

Mixed agonist/antagonist opioid analgesics: From a theoretical perspective, mixed agonist/antagonist opioid analgesics (e.g., pentazocine and buprenorphine) should NOT be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect or may precipitate withdrawal symptoms.

Monoamine oxidase inhibitors (MAOIs): MAOIs intensify the effects of morphine and other opioid drugs which can cause anxiety, confusion and significant depression of respiration, sometimes leading to coma. Morphine should not be given to patients taking MAOIs or within 14 days of stopping such treatment. It is unknown whether there is an

interaction between the new selective MAOIs (e.g., moclobemide and selegiline) and morphine. Therefore, caution is advised with such drug combinations.

Cimetidine and other H₂ receptor antagonists: There is a report of confusion and severe respiratory depression when a haemodialysis patient was administered morphine and cimetidine.

A potentially lethal interaction between cimetidine and morphine, in which the patient exhibited apnoea, a significantly reduced respiratory rate and suffered a grand mal seizure, has been reported. Administration of naloxone increased the respiratory rate; however, confusion, disorientation, generalised twitching and periods of apnoea persisted for 80 hours. Confusion has also been associated with concomitant use of ranitidine and morphine.

Diuretics: Morphine reduces the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with prostatism.

Phenothiazines: The analgesic effect of morphine is potentiated by chlorpromazine.

Amphetamines: Dexamphetamine and other amphetamines may enhance the analgesic effects, and decrease the sedation and lack of alertness caused by morphine.

Anticoagulants: Morphine may potentiate the anticoagulant activity of coumarin anticoagulant agents.

Metoclopramide: Morphine may antagonise the effects of metoclopramide on gastrointestinal motility. Intravenous metoclopramide antagonises the effects of morphine on gastric emptying.

Zidovudine: Morphine may alter the metabolism of zidovudine, by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism. Zidovudine and morphine should therefore not be administered concurrently, because the toxicity of either or both of these drugs may be increased.

Ritonavir: Ritonavir may increase the activity of glucuronyl transferases and co-administration with morphine may result in decreased morphine serum levels and possible loss of analgesic efficacy.

Oral drugs: Morphine delays gastric emptying, so may affect the absorption of orally administered drugs. For example, morphine delays the absorption of paracetamol, mexiletine and P2Y₁₂ inhibitors.

Anticholinergic agents: Concurrent administration of morphine and anticholinergic agents or other drugs with anticholinergic activity may increase the risk of severe constipation; this may lead to paralytic ileus and/or urinary retention.

Antidiarrhoeal agents: Concurrent administration of morphine and antidiarrhoeal agents with antiperistaltic actions may increase the risk of severe constipation and CNS depression.

Opioid antagonists: Naloxone antagonises the analgesic, CNS and respiratory depressive

effects of morphine, and may precipitate withdrawal in patients who are physically dependent on opioids.

Naltrexone blocks the therapeutic effects of opioids, so should be discontinued several days prior to elective surgery if administration prior to, during, or following surgery is unavoidable. Administration of naltrexone to a patient who is physically dependent on morphine will precipitate withdrawal symptoms.

P2Y₁₂ inhibitors:

Clinical Impact	The co-administration of oral P2Y ₁₂ inhibitors and with morphine can decrease the absorption and peak concentration of oral P2Y ₁₂ inhibitors and delay the onset of the antiplatelet effect, due to morphine’s effect on delay of gastric emptying.
Intervention	Consider the use of a parenteral antiplatelet agent in the setting of acute coronary syndrome requiring co-administration of morphine.
Examples of P2Y₁₂ inhibitors include but are not limited to	Clopidogrel, prasugrel, ticagrelor

Serotonergic drugs: The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. Drugs that affect the serotonergic neurotransmitter system include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT₃ receptor antagonists, and MAOIs.

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

Prolonged use of opioids may result in impairment of reproductive function, including fertility and sexual dysfunction in both sexes, and irregular menses in women.

Use in pregnancy (Category C)

Morphine has been associated with fetal CNS defects in rodent studies. It is not known whether morphine can cause fetal harm in humans when administered during pregnancy. Pregnant patients should only be given morphine when the benefits clearly outweigh potential risks to the fetus.

Long term use of morphine during pregnancy may result in a neonatal opioid withdrawal state. Babies born to mothers who are physically dependent on morphine may also be physically dependent on the drug.

Morphine crosses the placenta, and can produce respiratory depression in the neonate if it is administered during labour. Infants born to mothers receiving opioid analgesics during labour should be observed closely for signs of respiratory depression. In such infants a specific

opioid antagonist, naloxone hydrochloride, should be available for reversal of opioid induced respiratory depression.

Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

Use in labour/delivery

Morphine is not recommended for use in women during and immediately before labour. The effects of opioid analgesics are unpredictable. They may prolong labour by temporarily reducing the strength, duration and frequency of uterine contractions, or conversely they may tend to shorten labour by increasing the rate of cervical dilatation.

Use in lactation

Morphine is excreted in human milk and breast-feeding is not recommended while a patient is receiving morphine. Withdrawal symptoms have been observed in breast-fed infants when maternal administration of morphine sulfate pentahydrate is stopped.

4.7 Effects on Ability to Drive and Use Machines

Morphine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery.

4.8 Adverse Effects (Undesirable Effects)

The adverse effects caused by morphine are essentially the same as those observed with other opioid analgesics. They include the following major hazards: respiratory depression, apnoea and to a lesser degree circulatory depression, respiratory arrest, shock and cardiac arrest.

Most common adverse effects: Constipation, light headedness, dizziness, sedation, nausea, vomiting, sweating, dysphoria and euphoria.

Sedation: Most patients receiving morphine will experience initial drowsiness. This usually disappears in three to five days and is not a cause for concern unless it is excessive, or accompanied with unsteadiness or confusion. Excessive or persistent sedation should be investigated. Factors to be considered should include: concurrent sedative medications, the presence of hepatic or renal insufficiency, exacerbated respiratory failure, tolerance to the dose used, especially in older patients, disease severity and the patient's general condition. If the dose of morphine has been reduced and pain is not adequately controlled, the dose may be carefully increased again after a few days.

Dizziness and unsteadiness may be associated with morphine induced postural hypotension, particularly in elderly or debilitated patients. The dosage should be adjusted according to individual needs but, because of reduced clearance, dosage may be lower in patients over 50 years of age.

Nausea and vomiting: Nausea and vomiting are common after single doses of morphine or as an early undesirable effect of regular opioid therapy. The prescription of a suitable antiemetic should be considered. The frequency of nausea and vomiting usually decreases

within a week or so but may persist due to opioid induced gastric stasis. Metoclopramide is often useful in such patients.

Constipation: Virtually all patients suffer from constipation while taking opioids on a chronic basis. Some patients, particularly elderly, debilitated or bedridden patients, may become impacted. Patients must be cautioned accordingly and laxatives, softeners and other appropriate treatments should be initiated at the beginning of opioid therapy.

Other adverse effects include:

Cardiovascular: Flushing of the face, chills, tachycardia, bradycardia, palpitations, faintness, syncope, hypotension and hypertension.

Central nervous system: Euphoria, dysphoria, weakness, headache, restlessness, anxiety, agitation, tremor, uncoordinated muscle movements, insomnia, dizziness, vertigo, delirium, confusional symptoms and occasionally hallucinations, allodynia and hyperalgesia.

Gastrointestinal: Dry mouth, anorexia, constipation, cramps, laryngospasm, colic, taste alterations and biliary tract cramps and biliary spasm.

Genitourinary: Urinary retention or hesitancy, ureteric spasm, reduced libido or potency, amenorrhoea, erectile dysfunction and hypogonadism.

Endocrine: A syndrome of inappropriate antidiuretic hormone secretion characterised by hyponatraemia secondary to decreased free-water excretion may occur (monitoring of electrolytes may be necessary). Morphine stimulates prolactin release, and may also cause hyperglycaemia.

Visual disturbances: Blurred vision, nystagmus, diplopia and miosis.

Allergic: Pruritus, urticaria, other skin rashes including contact dermatitis, and oedema. Allergic reactions may be due to histamine release, and may be more frequent in asthmatic patients. Anaphylactic reactions following intravenous injection have been reported rarely.

Local effects: Pain at injection site; local tissue irritation and induration following subcutaneous injection, particularly when repeated.

Dependence/tolerance: Physical dependence and tolerance may develop with long term use of morphine.

Withdrawal (abstinence) syndrome: Chronic use of opioid analgesics may be associated with the development of physical dependence, with or without psychological dependence. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered.

Withdrawal symptoms that may be observed after discontinuation of opioid use include: body aches, diarrhoea, piloerection, anorexia, nervousness or restlessness, rhinorrhoea, sneezing, tremors or shivering, abdominal colic, nausea, sleep disturbance, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate dose adjustments and gradual withdrawal these symptoms are usually mild.

4.9 Overdose

Symptoms

Overdosage with morphine is characterised by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), 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

Immediate attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation.

In patients physically dependent on opioids, respiratory support is the first line of treatment. In these patients, the use of naloxone is potentially dangerous.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

The opioid antagonist, naloxone, is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to opioids. The recommended adult dose of naloxone for the treatment of severe opiate induced respiratory depression is 0.4 to 2 mg intravenously every 2 to 3 minutes as necessary, simultaneously with assisted respiration.

For children, the initial dose recommended is 0.01 mg/kg naloxone. A response should be seen after 2 to 3 doses. Note the duration of action of naloxone is usually shorter than that of morphine and thus the patient should be carefully observed for signs of CNS depression returning.

If the response to naloxone is suboptimal or not sustained, additional naloxone may be administered as needed, or given by continuous intravenous infusion to maintain alertness and respiratory function. There is no information available about the cumulative dose of naloxone that may be safely administered.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdosage.

Naloxone should be administered cautiously to persons who are known or suspected to be physically dependent on morphine. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If it is necessary to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Morphine toxicity may be a result of overdosage but because of the large inter-individual variation in sensitivity to opioids it is difficult to assess the exact dose of any opioid that is

toxic or lethal. The toxic effects of morphine tend to be overshadowed by the presence of pain or tolerance. Patients having chronic morphine therapy have been known to take in excess of 3,000 mg/day with no apparent toxic effects being present.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of action

Morphine is the principal alkaloid of opium. Morphine acts as an agonist, binding to receptors in the brain, spinal cord and other tissues. These sites have been classified as mu receptors and are widely distributed throughout the central nervous system being present in highest concentration in the limbic system.

Morphine exerts its primary effects in the central nervous system and organs containing smooth muscle.

Morphine produces many effects including analgesia, decreased gastrointestinal motility, respiratory depression, drowsiness, changes in mood and alterations of the endocrine and autonomic nervous systems.

Nausea and vomiting may occur through direct stimulation of the chemoreceptor trigger zone (CTZ).

Urinary retention may occur due to increased bladder sphincter tone.

Clinical trials

Chinese subjects given intravenous morphine have a higher rate of clearance when compared to white subjects (1852 ± 116 mL/min vs. 1495 ± 80 mL/min) because of an increase in the partial metabolic clearance by glucuronidation.

5.2 Pharmacokinetic Properties

Absorption

Absorption of morphine sulfate pentahydrate after intramuscular and subcutaneous injection is fairly rapid with peak analgesia occurring 30 to 60 minutes and 50 to 90 minutes after injection via the respective routes. Peak analgesia occurs within 20 minutes after intravenous administration.

Distribution

Morphine is distributed throughout the body, but particularly to parenchymatous tissue such as kidney, lung, liver and spleen. Lower concentrations are found in skeletal muscle and brain tissue. Morphine diffuses across the placenta and trace amounts are found in sweat and breast milk. About 35% is protein bound, mainly to albumin.

Metabolism

Morphine is metabolised principally in the liver by conjugation with glucuronic acid. The principal metabolites are morphine-3-glucuronide and morphine-6-glucuronide. Morphine-6-glucuronide is pharmacologically active and has a half-life somewhat longer than morphine.

Excretion

Elimination half-life from serum is approximately 1.5 to 2 hours in healthy subjects and 90% of the dose is recovered in urine within 24 hours. Approximately 7 to 10% of the dose is recovered in faeces, the majority after conjugation and excretion via bile.

5.3 Preclinical Safety Data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium chloride

Water for injections

Hydrochloric acid

6.2 Incompatibilities

A solution of thiopentone and morphine forms an inactive preparation.

6.3 Shelf Life

Stability in solution

DBL Morphine Sulfate Injection BP should be used within 24 hours of opening, in order to avoid the risk of microbial contamination.

6.4 Special Precautions for Storage

Store below 25°C. Protect from light.

6.5 Nature and Contents of Container

DBL Morphine Sulfate Injection BP is available in coloured glass ampoules in the following presentations:

Strength	Pack Sizes
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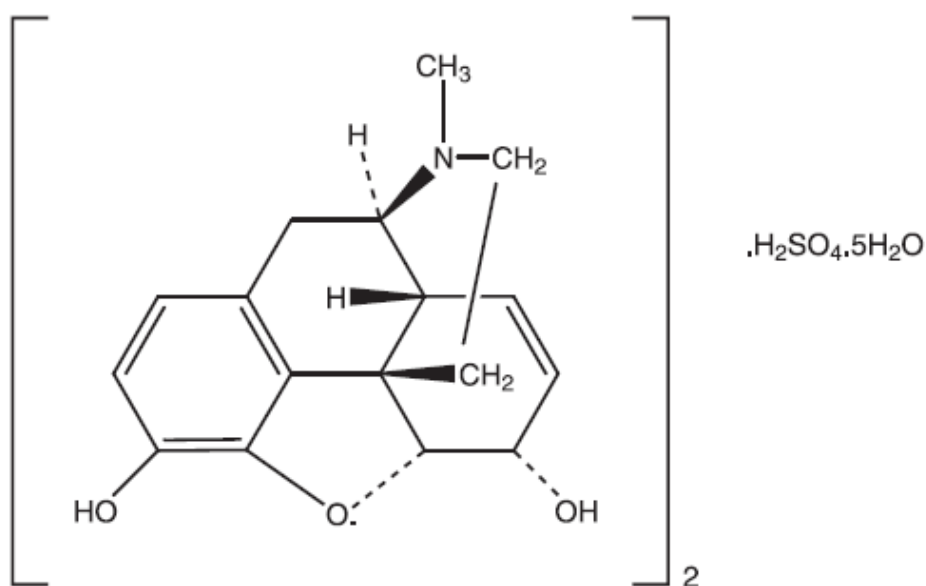
5 mg/1 mL	5's
10 mg/1 mL	5's and 50's
15 mg/1 mL	5's and 50's
30 mg/1 mL	5's

Not all presentations may be available locally.

6.6 Physicochemical Properties

Chemical structure

The structural formula of morphine sulfate pentahydrate is shown below:



CAS number

6211-15-0

7. NAME AND ADDRESS OF THE PRODUCT OWNER

Hospira Australia Pty Ltd
1 Lexia Place
Mulgrave VIC 3170
Australia

MOR-SIN-1219/0

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