**DBL™ MORPHINE TARTRATE INJECTION**

**Name of medicine**
Morphine tartrate

**Presentation**
DBL™ Morphine Tartrate Injection is a clear, colourless to almost colourless, sterile solution containing morphine tartrate trihydrate 80 milligrams/mL [equivalent to morphine sulphate pentahydrate 78 milligrams/mL] and sodium metabisulphite 1 milligram/mL in water for injections. The pH of the solution ranges between 4.0 and 5.0.

Morphine tartrate is a crystalline powder, which is soluble in 11 parts of water, slightly soluble in alcohol, and practically insoluble in chloroform, ether and carbon disulfide.

**Uses**

**Actions**
Morphine, the principal alkaloid of opium, is an opioid analgesic. It has agonist activity, binding to receptors in the brain, spinal cord and other tissues. Morphine is most active at the mu receptors, but is also active at the kappa receptors and may have some agonist activity at the delta receptors. The mu receptors are widely distributed throughout the central nervous system, particularly in the limbic system, thalamus, striatum, hypothalamus and midbrain, and in the dorsal horn of the spinal cord. Kappa receptors are localised primarily in the cerebral cortex and spinal cord, while delta receptors occur in the limbic system.

Morphine exerts its primary effect on the central nervous system (CNS) and on organs containing smooth muscle, including the intestines.

Morphine produces many pharmacological effects including analgesia, decreased gastrointestinal motility, respiratory depression, cough suppression, drowsiness, miosis, mood changes including euphoria and dysphoria, reduction in body temperature, and alterations in both the endocrine system and autonomic nervous system.

Cough suppression is mediated through a direct effect on the medullary centre. Respiratory depression results from reduced responsiveness of the respiratory centre to carbon dioxide. Nausea and vomiting may occur through direct stimulation of the chemoreceptor trigger zone. Urinary retention may occur due to increased bladder sphincter tone. Biliary tract pressure may occur as a result of morphine induced spasm of the sphincter of Oddi. Constipation is secondary to the action of morphine on bowel wall nerve plexuses.

Morphine tartrate has the same pharmacological activity as other morphine salts.

**Pharmacokinetics**

**Absorption:** Absorption of morphine after intramuscular and subcutaneous injection is fairly rapid, with peak analgesia occurring 30 to 60 minutes after intramuscular injection and 50 to 90 minutes after subcutaneous injection. Peak analgesia occurs within 20 minutes following intravenous administration.

**Distribution:** Morphine is distributed throughout the body, but particularly to parenchymatous tissue such as the kidneys, lungs, 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. Only small quantities of morphine cross the blood brain barrier. 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. Metabolism to morphine-3,6-diglucuronide occurs to a limited extent. Morphine-3-glucuronide is pharmacologically inactive and morphine-6-glucuronide is pharmacologically active. Other active metabolites include codeine, normorphine, and morphine-ethereal sulfate.
Excretion: The serum elimination half-life is approximately 1.5 to 2 hours in healthy subjects. About 90% of the dose is excreted in the urine within 24 hours. Approximately 7 to 10% of the dose is recovered in the faeces, the majority after conjugation and excretion via bile. Morphine-6-glucuronide has a longer half-life than morphine. In patients with renal impairment, accumulation of morphine-6-glucuronide occurs, which can result in enhanced and prolonged opiate activity.

Indications
Morphine tartrate is indicated for the symptomatic relief of severe and intractable pains of various categories, in terminal cancer patients.

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

DBL™ Morphine Tartrate Injection should be administered by subcutaneous, intramuscular or slow intravenous injection.

Adults
The usual adult dose by intramuscular or subcutaneous injection is 5 to 20 milligrams. Doses may be repeated every 4 to 6 hours.

Morphine may be administered intravenously when a rapid onset of action is desired. The usual adult dose is 2.5 to 15 milligrams diluted in 4 to 5 mL of water for injections given slowly over 4 to 5 minutes.

The dose should be reduced in elderly patients, those with respiratory impairment and in patients receiving other CNS depressant medication. In severe or chronic pain, the dose may need to be adjusted according to the response and tolerance of the patient.

Dosage reduction may be necessary in patients with renal or hepatic impairment (see PRECAUTIONS – Use with impaired renal or hepatic function).

Children
Morphine is given by intramuscular or subcutaneous injection in doses of 0.1 to 0.2 milligrams/kg bodyweight to a maximum of 15 milligrams. Doses 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 milligrams/kg, incrementally over 5 to 15 minutes. Repeat intravenous dosing is unsubstantiated as a method of analgesia in children.

Morphine 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 CONTRAINDICATIONS).

Note
Morphine tartrate contains almost an equivalent amount of morphine base per milligram as morphine sulphate. Therefore, the two preparations may be used interchangeably.

Continuous intravenous infusion
Morphine may be administered by continuous intravenous infusion using a suitable controlled rate infusion pump or syringe driver. The dosage of morphine should be titrated according to the patient’s analgesic requirements and previous opioid 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 milligrams/hour after adequate analgesia has been established.

For children, the recommended dose by intravenous infusion is 0.01 to 0.05 milligrams/kg/hour of morphine, to a maximum of 4 milligrams/hour.

An opioid antagonist and equipment for artificial ventilation should 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, the patient depresses a button, and a dose of morphine is administered intravenously. If the patient depresses 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 milligrams morphine have been given via PCA using a lockout interval of 6 to 10 minutes. Some syringe pumps also deliver a background continuous infusion of morphine at a basal rate, along with the self-administered dose of morphine. A dose of 1 milligram/hour morphine is often used in adults as a background infusion. 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 milligrams/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. A background infusion dose of 0.015 milligrams/kg/hour morphine has been 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.

Close monitoring is required, as the use of techniques such as PCA with background continuous infusion are associated with a higher rate of adverse effects.

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 may be inadequate or impractical in the terminally ill patient.

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

For cancer pain, morphine should be given regularly, in most instances every 4 hours. The basis of pain control with parenteral morphine should be regular scheduling rather than on an ‘as required’ or PRN order. Patients requiring high doses of morphine usually need to be awakened for medication during the night to prevent morning pain.

Morphine dosage increase
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 four to five 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.
Contraindications
Morphine alkaloids are contraindicated in patients with a known hypersensitivity to morphine or other opioids. DBL™ Morphine tartrate injection is contraindicated in patients who are hypersensitive to sodium metabisulfite as sodium metabisulfite may cause allergic type reactions, including anaphylaxis and life-threatening or less severe asthmatic episodes in certain susceptible individuals. The overall prevalence of sulfite sensitivity in the general population is unknown but probably low; such sensitivity appears to occur more frequently in asthmatic than in non-asthmatic individuals.

Morphine is also contraindicated in the following situations:
- premature infants or during labour or delivery of premature infants;
- patients with respiratory depression, especially in the presence of cyanosis and/or excessive bronchial secretions;
- bronchial asthma or other obstructive airways disease;
- other conditions where respiratory reserve is depleted, such as severe emphysema, chronic bronchitis or kyphoscoliosis;
- cor pulmonale;
- diabetic acidosis where there is a danger of coma;
- acute alcoholism or delirium tremens;
- heart failure secondary to chronic pulmonary disease;
- cardiac arrhythmias;
- head injuries;
- raised cerebrospinal or intracranial pressure;
- convulsive states such as status epilepticus, tetanus or strychnine poisoning;
- severe CNS depression;
- brain tumour;
- severe liver disease or incipient hepatic encephalopathy;
- gastrointestinal obstruction;
- suspected surgical abdomen;
- biliary colic;
- following operations on the biliary tract or surgical anastomosis.

Morphine should not be given to patients taking monoamine oxidase inhibitors or within fourteen days of stopping such treatment (see WARNINGS and PRECAUTIONS – Interactions with other drugs).

Continuous intravenous infusion of morphine is contraindicated in patients with hepatic or renal disease (see WARNINGS and PRECAUTIONS – Use with impaired renal or hepatic function).

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

Warnings and precautions
Large doses and/or rapid administration of morphine may produce rapid onset of respiratory depression, bradycardia, or even cardiac arrest.

Morphine may cause drowsiness, and may impair the mental and/or physical abilities needed to perform potentially hazardous tasks, such as driving a car or operating machinery. Patients should be warned of these effects. Patients should also be warned of the potential for additive effects if morphine is taken with other CNS depressants (see Interactions with other drugs).

Drug Dependence and Tolerance
Morphine can produce drug dependence and therefore has the potential to be 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 discontinuation. 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 physically dependent patients may precipitate an acute withdrawal syndrome, including convulsions.

**Gastrointestinal Motility**
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.

**Other Special Risk Patients**
Morphine should be given with caution or in reduced amounts to patients with adrenocortical insufficiency (e.g. Addison’s disease), impaired liver function, shock, hypothyroidism, myxoedema, prostatic hypertrophy, urethral stricture, impaired pulmonary or renal function and in aged or debilitated patients. Caution should also be observed if morphine is administered to patients with toxic psychosis or myasthenia gravis. Patients with reduced circulating volume or impaired myocardial function should be carefully observed for orthostatic hypotension.

**Head Injury and Increased Intracranial Pressure**
Morphine should be used with extreme caution in patients with head injuries, other intracranial lesions and raised intracranial pressure, as respiratory depression and potential to increase cerebrospinal fluid (CSF) pressure may be exaggerated, thereby complicating the clinical course. Morphine may produce confusion, miosis, vomiting and other side effects which obscure the clinical course in patients with head injuries. Morphine should only be used in these patients if it is considered essential.

**Respiratory Depression**
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 reactions, including confusion, miosis and vomiting, which may obscure the clinical course of patients with head injuries. Morphine should therefore be used with extreme caution in these patients.

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 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 CONTRAINDICATIONS).

**Hypotensive Effect**
Morphine administration may cause severe hypotension in patients whose ability to maintain adequate blood pressure has been compromised by a reduced blood volume or concurrent administration of other drugs with hypotensive effects such as phenothiazines or anaesthetics. Morphine may produce orthostatic hypotension in ambulatory patients.

**Acute Abdominal Condition**
The administration of morphine or other opioids may obscure the diagnosis and 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.

**Seizures**
High doses of morphine may cause seizures; therefore, patients with known seizure disorders should be carefully observed, especially if doses are increased in response to tolerance to the drug.

**Renal or Hepatic Disease**
Caution should be observed when morphine is administered to patients with impaired renal function (see Use with impaired renal or hepatic function).
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.

Biliary Surgery or Pancreatitis
Morphine may cause spasm of the biliary tract and sphincter of Oddi and should be used only when necessary, and with caution, in patients with biliary colic, operations on the biliary tract and acute pancreatitis.

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 children
Morphine should be administered with extreme care to newborn infants, as its safety and efficacy have not been established. Neonates have an enhanced susceptibility to the respiratory depressant effects of morphine. Morphine should not be administered to premature infants (see CONTRAINDICATIONS).

Use in the elderly
Morphine should be administered with caution and in reduced dosages to elderly or debilitated patients, as respiratory depression occurs more frequently in these patients.

Use with impaired renal or hepatic function
Morphine should be given with caution or in reduced amounts to patients with impaired renal or hepatic function, as morphine is principally metabolised in the liver and excreted in the urine (see PHARMACOLOGY – Pharmacokinetics).

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.

Continuous intravenous infusion of morphine is contraindicated in patients with hepatic or renal disease (see CONTRAINDICATIONS).

Pregnancy and Lactation
Use in Pregnancy
Category C

Opioid analgesics may cause respiratory depression in the newborn infant. Withdrawal symptoms in newborn infants have been reported with prolonged use of this class of drugs.

Morphine has been associated with foetal CNS defects in rodent studies. It is not known whether morphine can cause foetal harm in humans when administered during pregnancy. As safety in pregnancy has not been established, morphine administration is not recommended during pregnancy unless the benefits clearly outweigh any potential risk to the foetus.

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.

Use of morphine during and immediately before labour is not recommended, as its effects are unpredictable. Morphine may prolong labour by temporarily reducing the strength, duration and frequency of uterine contractions, or conversely, may tend to shorten labour by increasing the rate of cervical dilatation.

Morphine crosses the placenta and may produce respiratory depression in the neonate if it is administered during labour. Morphine should only be administered during the last 2 to 3 hours before expected delivery if the expected benefits to the mother outweigh the risk to the foetus.
Infants born to mothers who have received opioid analgesics during labour should be observed closely for signs of respiratory depression. Naloxone, a specific opioid antagonist, should be available for reversal of opioid induced respiratory depression if necessary.

**Use in lactation**
Morphine is excreted in breast milk; therefore, administration of morphine to women who are breast-feeding is not recommended. Withdrawal symptoms have been observed in breast-fed infants following discontinuation of maternal morphine administration.

**Other**
**Carcinogenicity, mutagenicity, impairment of fertility**
The carcinogenic or mutagenic potential of morphine has not been established.

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

**Effect on laboratory tests**
Morphine delays gastric emptying, thereby invalidating test results in gastric emptying studies.

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

**Adverse effects**
The major adverse reactions associated with morphine include the following: respiratory depression, apnoea, and to a lesser degree circulatory depression. Respiratory arrest, shock and cardiac arrest have occurred following morphine administration.

**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 clears in three to five days and is usually not a cause for concern unless it is excessive, or associated with unsteadiness or confusion. Excessive or persistent sedation should be investigated. Possible causes include concurrent sedative medications, the presence of hepatic or renal insufficiency or exacerbated respiratory failure, tolerance to the dose used, especially in older patients, and the patient's general condition and the severity of the disease. If it is necessary to reduce the dose of morphine, but the 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, the appropriate dosage may be lower in patients over 50 years of age.

**Nausea and vomiting:** Nausea and vomiting frequently occur after single doses of morphine or as an early undesirable effect of regular opioid therapy. Routine administration of a suitable antiemetic should be considered if prolonged morphine therapy is to be instituted. The frequency of nausea and vomiting usually decreases within a week or so but may persist due to opioid induced gastric stasis.

**Constipation:** Chronic morphine administration will cause constipation in virtually all patients. Some patients, particularly elderly, debilitated or bedridden patients, may become impacted. Patients must be cautioned accordingly. An appropriate regimen of bowel management should be initiated when opioid therapy is commenced.

**Other adverse effects**
**Cardiovascular:** Facial flushing, chills, tachycardia, bradycardia, palpitations, faintness, syncope, hypotension.
Central nervous system: Change of mood, euphoria or dysphoria, weakness, headache, restlessness, anxiety, agitation, tremor, uncoordinated muscle movements, insomnia, dizziness, vertigo, delirium, confusion or disorientation, transient hallucinations.

Gastrointestinal: Dry mouth, anorexia, constipation, cramps, laryngospasm, colic, taste alterations, 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. If this occurs, electrolyte monitoring may be necessary. Morphine stimulates prolactin release, and may also cause hyperglycaemia.

Ocular: Visual disturbances, blurred vision, nystagmus, diplopia, miosis.

Allergic: Pruritus, urticaria, other skin rashes including contact dermatitis, 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.

Dependence/tolerance: In long term use, physical dependence and tolerance may develop.

Withdrawal (abstinence) syndrome: Physical dependence, with or without psychological dependence, may occur as a result of chronic use of opioid analgesics. A withdrawal syndrome may be precipitated if opioid administration is discontinued suddenly, or if an opioid antagonist is administered.

Withdrawal symptoms include body aches, diarrhoea, piloerection, anorexia, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, 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.

Interactions
Acidifying agents generally increase the clearance of morphine, thus reducing its effects, while alkalising agents decrease clearance and so potentiate the effects of morphine.

CNS depressants: The depressant effects of morphine are enhanced by other drugs with CNS depressant activity, including other opioids, alcohol, sedatives, antihistamines, tranquillisers (e.g. phenothiazines, butyrophenones), tricyclic antidepressants, chloral hydrate, anaesthetics, glutethimide and beta blockers.

Morphine should be used with caution and in a reduced dosage if it is used concurrently with other drugs with CNS depressant activity, as the risk of respiratory depression, hypotension and profound sedation or coma is increased.

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

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: The hypotensive effects of antihypertensive drugs and hypotension producing drugs maybe potentiated with the concurrent administration of morphine leading to increased risk of orthostatic hypotension.

Phenothiazines: Concurrent administration of morphine with some phenothiazines may increase the risk of morphine induced hypotension. Chlorpromazine may enhance the analgesic effects of morphine.

Amphetamines: Dexamphetamine and other amphetamines may enhance the analgesic effects, and decrease the sedation and lack of alertness caused by morphine.
**Muscle relaxants:** Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants, and may produce an increased degree of respiratory depression.

**Mixed agonist/antagonist opioid analgesics:** Pentazocine and buprenorphine, should theoretically not be administered concurrently with morphine, as they may reduce the analgesic effect of morphine, or may precipitate withdrawal symptoms.

**Monoamine oxidase inhibitors (MAOIs):** Non-selective monoamine oxidase inhibitors (MAOIs) enhance the effects of morphine, and can cause anxiety, confusion and significant respiratory depression, sometimes leading to coma. Morphine should not be given to patients taking MAOIs or within fourteen days of stopping such treatment (see **CONTRAINDICATIONS**). Caution is advised with selective MAOIs (e.g. moclobemide and selegeline), as it is not known whether these drugs interact with morphine.

**Cimetidine and other H₂ receptor antagonists:** 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.

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

**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.

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

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

**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.

Atropine may counteract morphine induced miosis.

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

Doxapram may antagonise morphine induced respiratory 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 morphine administration before, during, or following surgery is unavoidable. Administration of naltrexone to a patient who is physically dependent on morphine will precipitate withdrawal symptoms.
**Overdosage**

**Symptoms**

Opioid analgesic overdosage usually produces central nervous system depression ranging from stupor to a profound coma; respiratory depression which may progress to Cheyne-Stokes respiration and/or cyanosis; cold, clammy skin and/or hypothermia; flaccid skeletal muscles; bradycardia; and hypotension. In patients with severe overdosage, particularly following rapid intravenous opioid administration, apnoea, circulatory collapse, cardiac arrest, respiratory arrest and death may occur. Complications such as pneumonia, shock, and/or pulmonary oedema may also prove fatal. Although miosis is characteristic of overdosage with morphine, mydriasis may occur in terminal narcosis or severe hypoxia.

Overdosage may be caused inadvertently by delayed absorption when repeated doses of opioid analgesics are administered intramuscularly or subcutaneously to a patient with hypothermia, shock, hypotension, or any other condition that might impair circulation. When circulation is restored in these patients, large amounts of the opioid are absorbed into the blood stream. Therefore, such patients should receive intravenous rather than subcutaneous or intramuscular injections with the consideration that intravenous administration may increase the already severe cardiorespiratory impairment.

**Treatment**

In the treatment of opioid overdosage, especially in the presence of apnoea, primary attention should be given to re-establishment of adequate respiratory exchange by maintenance of adequate airway, control of respiration and oxygen administration.

Opioid-induced respiratory depression may be treated with an opioid antagonist. Naloxone, a pure antagonist, is a specific antidote against the respiratory depression resulting from opioid overdose. Administer intravenous naloxone (e.g. 0.4 to 2 milligrams) which may be repeated at 2 to 3 minute intervals. A response should be seen after 2 to 3 doses. For children, the recommended initial dose of naloxone is 0.01 milligrams/kg. 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.

In severe toxicity the cardiovascular system is usually depressed and requires supportive treatment. If hypotension is due to vasodilatation, then plasma expansion or even vasopressors may be required. Additional measures include support of electrolyte balance, maintenance of normal temperature, catheterisation of the bladder to avoid distension and symptomatic treatment for itching, nausea, vomiting, headache and confusion during the recovery period.

Acidification of the urine will enhance excretion of absorbed drug.

**NOTE:** In an individual physically dependent on opioids, the administration of the usual dose of an opioid antagonist (eg. naloxone) will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of opioid antagonists in such individuals should be avoided if possible. If an opioid antagonist must be used to treat serious respiratory depression in the physically dependent patient, only 10% to 20% of the usual initial dose of the antagonist should be administered.

**Pharmaceutical precautions**

**Incompatibilities**

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

A solution of thiopentone and morphine forms an inactive preparation.

Morphine tartrate, alone or mixed with chlorpromazine hydrochloride, metoclopramide hydrochloride or morphine sulphate in plastic syringes, was found to retain potency for a period of 48 hours, when stored at room temperature in the presence of light. It is recommended, however, that the injection is used within 24 hours of preparation to reduce the risk of microbiological contamination.
**Special Precautions for Storage**
Store below 25°C. Protect from light.

**STABILITY**
**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.

**Medicine classification**
Class B1 Controlled Drug

**Package quantities**
**DBL™ Morphine Tartrate Injection**

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<th>Strength</th>
<th>Pack*</th>
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<tr>
<td>120 milligrams/1.5 mL</td>
<td>5 ampoules</td>
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<tr>
<td>400 milligrams/5 mL</td>
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* Not all pack sizes may be marketed.

**Further information**
The chemical formula of morphine tartrate trihydrate is \((C_{17}H_{19}NO_3)_2C_4H_6O_6\cdot3H_2O\). Its molecular weight is 774.8 and its CAS registry number is 6032-59-3. The chemical structure of morphine tartrate trihydrate is shown below:

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**Date of preparation**
04 September 2015