

MORPHINE SULFATE

10 mg/mL Solution for Injection



WARNINGS

Limitations of use

Because of the risks associated with the use of opioids, morphine should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain (see **Section 4.4 Special Warnings and Precautions for Use**).

Hazardous and harmful use

Morphine poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see **Section 4.4. Special Warnings and Precautions for Use**).

Life-threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of morphine. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see **Section 4.4 Special Warnings and Precautions for Use**).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol

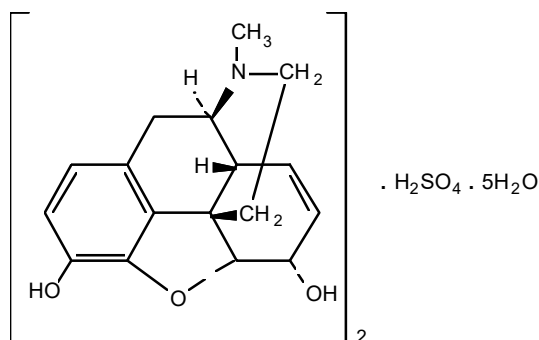
Concomitant use of opioids with other opioids analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, general anaesthetics, tranquilisers, beta blocker, or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while using morphine (see **Section 4.4 Special Warnings and Precautions for Use**).

1.0 PHARMACOLOGIC CATEGORY

Opioid Analgesic

2.0 DESCRIPTION

The structural formula of morphine sulfate is shown below:



CAS number: 6211-15-0

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

3.0 FORMULATION/COMPOSITION

Each mL of isotonic preparations of Morphine Sulfate Injection contains morphine sulfate 10 milligrams. This is a sterile solution of morphine sulfate 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 6.5 List of Excipients**.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

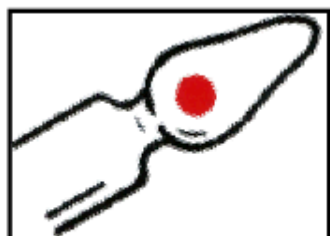
Morphine Sulfate Injection is indicated for the short-term management of severe pain for which other treatment options have failed, are contradicted, not tolerated or are otherwise inappropriate to provide sufficient management of pain.

Morphine Sulfate Injection may also be used as a pre-operative medication and as an analgesic adjunct in general anaesthesia.

4.2 Dosage 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.

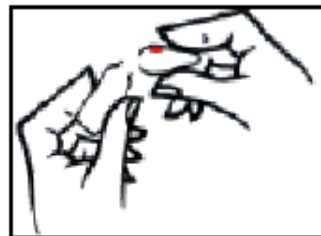
One Point Cut opening instructions



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

Morphine sulfate 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 milligrams diluted in 4 to 5 mL of Water for Injections given slowly over 4 to 5 minutes.

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

Morphine sulfate 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 milligrams/hour after adequate analgesia has been established.

In children, an infusion dose of 0.01 to 0.05 milligrams/kg/hour morphine to a maximum intravenous dose of 4 milligrams/hour 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 milligrams 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 milligram/hour 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 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. If a background infusion is employed, an infusion dose of 0.015 milligrams/kg/hour 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 utilizing 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 individualized 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 metabolized 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 Sulfate Injection should be given regularly around the clock, in most instances every 4 hours. The basis of pain control with Morphine Sulfate Injection 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 color in morphine solutions does not indicate toxicity or loss of potency or efficacy.

4.3 Contraindications

Morphine sulfate is contraindicated in the following situations:

- patients with known hypersensitivity to morphine or other opioids;
- patients with severe respiratory disease, acute respiratory disease, respiratory depression or insufficiency, especially in the presence of cyanosis and/or excessive bronchial secretion;
- patients with acute or severe bronchial asthma or other obstructive airways disease;
- 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 tumor;
- 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 labor 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

Hazardous and harmful use

Morphine Sulfate Injection contains the opioid morphine and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed morphine at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed morphine.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see **Sections 6.2 Storage Conditions** and **6.4 Special Precautions for Disposal and Other Handling**). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share morphine with anyone.

Accidental ingestion/exposure

Accidental ingestion or exposure of morphine, especially by children, can result in a fatal overdose of morphine. Patients and their caregivers should be given information on safe storage and disposal of unused morphine (see **Sections 6.2 Storage Conditions** and **6.4 Special Precautions for Disposal and Other Handling**).

Respiratory depression

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of morphine but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients, in patients with existing impairment of respiratory function, in those suffering from conditions accompanied by hypoxia or hypercapnia (e.g. chronic obstructive pulmonary disease; asthma), when even moderate therapeutic doses may significantly decrease pulmonary ventilation and in patients with hepatic and renal impairment. Morphine should therefore be used only in patients for whom its use is judged to be essential, with extreme caution and close monitoring (see **Section 4.2 Dosage and Method of Administration**). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see **Section 4.3 Contraindications**).

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.

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

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response (see **Section 4.2 Dosage and Method of Administration**).

Resuscitative equipment and opioid antagonist must be readily available.

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.

Serotonin syndrome (SS)

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 Interaction with Other Medicinal Products and Other Forms of Interaction**). Signs of SS may include clonus, agitation, diaphoresis, tremor, hyperreflexia, hypertonia and temperature elevation.

Cardiovascular instability

While low doses of intravenously administered morphine have little effect on cardiovascular stability, high doses are excitatory, resulting from sympathetic hyperactivity and increase in circulatory catecholamines. Have naloxone injection and resuscitative equipment immediately available for use in case of life-threatening or intolerable side effects and whenever morphine therapy is being initiated.

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.

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 anesthetics.

Morphine may produce orthostatic hypotension in ambulatory patients.

Shock patients

In patients with shock, impaired perfusion may prevent complete absorption following subcutaneous or intramuscular injection of morphine. Repeated administration may result in overdose due to an excessive amount of morphine suddenly being absorbed when circulation is restored.

Tolerance, dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid. 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.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced. Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate, increased heart rate, piloerection, sneezing, convulsions, and unexplained fever.

When discontinuing morphine in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see **Ceasing opioids and section 4.2 Dosage and Method of Administration**).

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see Tolerance, dependence and withdrawal). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been using, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks (see **Section 4.2 Dosage and Method of Administration**). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

Neonatal opioid withdrawal syndrome

Refer to **section 4.6 Fertility, Pregnancy and Lactation – Use in pregnancy – Category C**.

Use of opioids in chronic (long-term) non-cancer pain (CNCP)

Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should

only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see Hazardous and harmful use). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain, but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see Ceasing opioids).

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see Tolerance, dependence and withdrawal). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Adrenal insufficiency

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.

Delayed gastric emptying

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.

Acute abdominal conditions

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.

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, myxedema, 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 characterized by hypoxia, since even usual therapeutic doses of opioids may decrease respiratory drive to the point of apnea while simultaneously increasing airway resistance.

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of morphine with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, general anaesthetics, tranquilisers, beta blockers, or other CNS depressants should be reserved for patients for whom other treatment options are not possible. If a decision is made to prescribe morphine concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. 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.

Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while using morphine.

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. 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 concomitant CNS depressants including alcohol and illicit drugs (see **Section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**). If respiratory depression of any form occurs, consider decreasing the opioid dosage using best practices for opioid taper.

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 Interaction with Other Medicinal Products and Other Forms of Interaction**).

Use in hepatic impairment

Morphine may have a prolonged duration and cumulative effect in patients with 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**).

Use in renal impairment

Morphine may have a prolonged duration and cumulative effect in patients with kidney 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-**Other special risk patients**.

Pediatric 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**).

Morphine should not be administered via patient-controlled analgesia to children less than six years of age with poor cognitive function.

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} diosgenin. Morphine may constrict the sphincter of Oddi and increase biliary tract pressure, preventing delivery of Tc^{99m} diosgenin to the small bowel. These actions result in delayed visualization, and thus resemble obstruction of the common bile duct.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Acidifying agents generally increase the clearance of morphine, thus antagonizing its effects, while alkalizing 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 analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, general anesthetics, tranquilizers, beta blockers, or other CNS depressants, including 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. Patients should be cautioned accordingly.

Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact	Due to additive pharmacologic effect, the concomitant use with other opioids analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, general anesthetics, tranquilizers, beta blockers, 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	Other opioids analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, general anesthetics, tranquilizers, beta blockers, other CNS depressants, including alcohol.

Significant impairment of motor function has also 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: 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 (see **Section 4.3 Contraindications**). 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 hemodialysis patient was administered morphine and cimetidine.

A potentially lethal interaction between cimetidine and morphine, in which the patient exhibited apnea, a significantly reduced respiratory rate and suffered a grand mal seizure, has been reported. Administration of naloxone increased the respiratory rate; however, confusion, disorientation, generalized twitching and periods of apnea 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 antagonize the effects of metoclopramide on gastrointestinal motility. Intravenous metoclopramide antagonizes 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.

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

Opioid antagonists: Naloxone antagonizes 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 P2Y₁₂ inhibitors with morphine can decrease the absorption and peak concentration of oral P2Y₁₂ 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 monoamine oxidase inhibitors (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

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.

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.

Prolonged use of morphine during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. Babies born to mothers who are physically dependent on morphine may also be physically dependent on the drug. If prolonged use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Morphine crosses the placenta, and can produce respiratory depression in the neonate if it is administered during labor. Infants born to mothers receiving opioid analgesics during labor 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.

Morphine is not recommended for use in women during and immediately before labor. The effects of opioid analgesics are unpredictable. They may prolong labor by temporarily reducing

the strength, duration and frequency of uterine contractions, or conversely they may tend to shorten labor 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 is stopped.

4.7 Effects on Ability to Drive and Use Machines

Morphine may cause drowsiness and general impairment of coordination and may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. Ambulatory patients should be cautioned against driving or operating machinery.

4.8 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, apnea 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 using 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, amenorrhea, erectile dysfunction and hypogonadism.

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

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

Allergic: Pruritus, urticaria, other skin rashes including contact dermatitis, and edema. 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, diarrhea, piloerection, anorexia, nervousness or restlessness, rhinorrhea, 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 and Treatment

Symptoms

Overdosage with morphine is characterized 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, apnea, 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 milligrams intravenously every 2 to 3 minutes as necessary, simultaneously with assisted respiration.

For children, the initial dose recommended is 0.01 milligrams/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 milligrams/day with no apparent toxic effects being present.

5.0 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 versus 1495 ± 80 mL/min) because of an increase in the partial metabolic clearance by glucuronidation.

5.2 Pharmacokinetic Properties

Absorption

Absorption of morphine sulfate 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 metabolized 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 feces, the majority after conjugation and excretion via bile.

5.3 Preclinical Safety Data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-Life

Please see outer package for the expiry date.

6.2 Storage Conditions

Store at temperatures not exceeding 25°C. Protect from light.

6.3 Availability

Morphine Sulfate Injection is available in USP Type I, amber glass, one-point-cut ampoule x 1 mL (Box of 5's).

6.4 Special Precautions for Disposal and Other Handling

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

6.5 List of Excipients

Sodium chloride

Water for injections

Hydrochloric acid

6.6 Incompatibilities

A solution of thiopentone and morphine forms an inactive preparation.

7.0 FDA REGISTRATION NUMBER

DR-XY33322

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

18-May-2007

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Dangerous Drug Statement as per Republic Act. No. 9165:

DDB Regulation requires prescription and dispensing through a Special Prescription Form for Dangerous Drug by a current PDEA S2-licensed medical practitioner.

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