PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

[N] Morphine Sulfate Injection, USP

Sterile Solution for Injection: 2 mg / mL, 4 mg / mL and 10 mg / mL

in Simplist™ prefilled single use syringes

Intravenous, Intramuscular, and Subcutaneous

Narcotic Analgesic

Fresenius Kabi Canada Inc.
165 Galaxy Blvd., Suite 100
Toronto, ON
M9W 0C8

Date of Preparation: May 15, 2019

Submission Control Number: 215897

Table of Contents

[N] Morphine Sulfate Injection, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intravenous, Intramuscular, and Subcutaneous	Sterile Solution for Injection, 2 mg / mL, 4 mg / mL and 10 mg / mL in Simplist™ prefilled single use syringes	Sodium chloride, sodium citrate dihydrate, citric acid, edetate disodium, calcium chloride dihydrate, and water for injection

INDICATIONS AND CLINICAL USE

Adults
Morphine Sulfate Injection, USP administered by slow intravenous injection, is indicated for the relief of moderate to severe pain.

Morphine Sulfate Injection, USP is not indicated as an as-needed (prn) analgesic.

Geriatrics (> 65 years of age)
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy.

Pediatrics (<12 years of age)
The safety and efficacy of morphine sulfate has not been studied in the pediatric population. Therefore the use of Morphine Sulfate Injection, USP is not recommended in patients under 12 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance morphine sulfate or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).

- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders, such as those occurring in *status epilepticus*, tetanus, and strychnine poisoning.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with immediate release opioid formulations, Morphine Sulfate Injection, USP should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse

Morphine Sulfate Injection, USP poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing Morphine Sulfate Injection, USP and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS, Abuse and Misuse). Morphine Sulfate Injection, USP should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression may occur with use of Morphine Sulfate Injection, USP. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of Morphine Sulfate Injection, USP or following a dose increase. Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure

Accidental exposure of even one dose of Morphine Sulfate Injection, USP especially by children, can result in a fatal overdose of morphine sulfate (see DOSAGE AND ADMINISTRATION, Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of Morphine Sulfate Injection, USP during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGSAND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS)).

Interaction with Alcohol
Caution should be observed when administering Morphine Sulfate Injection, USP to patients who have been or are taking alcohol. Morphine Sulfate Injection, USP should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of Morphine Sulfate Injection, USP and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

General
Do not use unless solution is clear and package is undamaged. Morphine products may discolor over a period of time. No loss of analgesic potency and no increase in toxicity has ever been demonstrated for such discolored solutions.

Morphine Sulfate Injection, USP should be stored securely to avoid theft or misuse.

Morphine Sulfate Injection, USP should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking Morphine Sulfate Injection, USP as it may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further dose increase of morphine sulfate can occur at particularly high doses. A morphine sulfate dose reduction or change in opioid may be required.

Abuse and Misuse
Like all opioids, Morphine Sulfate Injection, USP is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, Morphine Sulfate Injection, USP should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as Morphine Sulfate Injection, USP should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Carcinogenesis and Mutagenesis

Long-term studies in animals have not been performed to evaluate the carcinogenic or the mutagenic potential of morphine. No long-term follow-up studies of patients receiving morphine epidurally have been conducted

Cardiovascular

Morphine sulfate administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. Morphine may product orthostatic hypotension in ambulatory patients. These patients should be monitored for signs of hypotension after initiating or titrating the dose of Morphine Sulfate Injection, USP.

The use of Morphine Sulfate Injection, USP in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression and should be avoided (see DOSAGE AND ADMINISTRATION).

Caution should be used in patients with atrial flutter and other supraventricular tachycardias due to a possible vagolytic action which may produce a significant increase in the ventricular response rate.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of Morphine Sulfate Injection, USP and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. However, psychic dependence is unlikely to develop when morphine is used for a short time for the relief of pain. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse. Physical dependence assumes clinically significant proportions only after several weeks of continued opioid use, although some mild degree of physical dependence may develop after a few days of opioid therapy. Tolerance is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include lacrimation, rhinorrhea, dilated pupils, irritability, body aches, diarrhea, goosebumps, loss of appetite, nausea, vomiting, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning. Treatment of the abstinence syndrome is primarily symptomatic and supportive, including maintenance of proper fluid and electrolyte balance (see ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

Use in Drug and Alcohol Addiction

Morphine sulfate is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to Morphine Sulfate Injection, USP; extreme caution and awareness are warranted to mitigate the risk.

Endocrine

Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Gastrointestinal Effects

Morphine sulfate and other morphine-like opioids have been shown to decrease bowel motility. Care should be exercised in patients with disorders of the biliary tract because circulating morphine may induce smooth muscle hypertonicity resulting in biliary colic. Morphine sulfate may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see CONTRAINDICATIONS).

Neonatal Opioid Withdrawal Syndrome (NOWS)

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug

by the newborn.

Morphine Sulfate Injection, USP is not recommended to be used in pregnant women, unless, in the judgement of the physician, the potential benefits outweigh the risks. If Morphine Sulfate Injection, USP was used during pregnancy, special attention to NOWS is warranted.

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Morphine Sulfate Injection, USP should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-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 DRUG 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 Sulfate Injection, USP 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 DRUG INTERACTIONS).

Morphine Sulfate Injection, USP should not be administered if patients have been or are consuming alcohol as it may increase the chance of experiencing dangerous side effects, including death (see CONTRAINDICATIONS; ADVERSE REACTIONS, Sedation; and DRUG INTERACTIONS).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

Morphine may aggravate pre-existing convulsive disorders. Convulsions may occur in individuals without a history of convulsive disorders if dosage is substantially escalated above recommended levels because of tolerance development.

Head Injury: The respiratory depressant effects of morphine sulfate, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, morphine sulfate may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, morphine sulfate must be used with extreme caution and only if it is judged essential (see CONTRAINDICATIONS).

Serotonin Syndrome: Morphine Sulfate Injection, USP could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotoninergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. Morphine Sulfate Injection, USP should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see DRUG INTERACTIONS).

Peri-Operative Considerations

Morphine Sulfate Injection, USP is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with Morphine Sulfate Injection, USP for at least 24 hours before the operation and Morphine Sulfate Injection, USP should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if Morphine Sulfate Injection, USP is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).
Morphine sulfate and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented. Morphine Sulfate Injection, USP should not be used in the early post-operative period (12 to 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

Psychomotor Impairment

Morphine Sulfate Injection, USP may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of morphine sulfate with other CNS depressants, including other opioids,

phenothiazine, sedative/hypnotics and alcohol.

Respiratory

Respiratory Depression: Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Morphine Sulfate Injection, USP should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see CONTRAINDICATIONS).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Morphine Sulfate Injection, USP the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with Morphine Sulfate Injection, USP and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

To reduce the risk of respiratory depression, proper dosing and titration of Morphine Sulfate Injection, USP are essential. Overestimating the Morphine Sulfate Injection, USP dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups; and DOSAGE AND ADMINISTRATION).

Indiscriminate use of morphine in asthma and pulmonary emphysema may, due to its drying action upon the respiratory tract mucosa, precipitate severe respiratory insufficiency resulting from increased viscosity of bronchial secretions and suppression of the cough reflex. Morphine Sulfate Injection, USP should be used with great caution in patients having an acute asthmatic attack.

Use in Patients with Chronic Pulmonary Disease: Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with Morphine Sulfate Injection, USP as in these patients, even usual therapeutic doses of Morphine Sulfate Injection, USP may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of Morphine Sulfate Injection, USP is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see CONTRAINDICATIONS).

Sexual Function/Reproduction

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see ADVERSE REACTIONS, Post-

Marketing Experience).

Special Populations

Special Risk Groups: Morphine Sulfate Injection, USP should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired hepatic or renal function, pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

Pregnant Women: Studies in humans have not been conducted. Morphine Sulfate Injection, USP crosses the placental barrier and is not recommended to be administered to pregnant women unless, in the judgement of the physician, potential benefits outweigh the risks.

Morphine sulfate administered a short of time (i.e., up to 4 hours) prior to delivery to women with no history of chronic abuse or dependence has been associated with a delay in initial respiration and transient respiratory depression in the neonate. Respiratory depression may be produced in the neonate even in its absence in the mother, presumably because of an immature blood-brain barrier in the neonate. The comparative fetal and neonatal respiratory depressant tendencies of equivalent analgesic doses of all drugs in this class have been determined.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal Opioid Withdrawal Syndrome (NOWS), unlike opioid withdrawal syndrome in adults, may be life-threatening (see WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS)).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

Labour, Delivery and Nursing Women: Since opioids can cross the placental barrier and are excreted in breast milk, Morphine Sulfate Injection, USP is not recommended to be used in nursing women and during labour and delivery unless, in the judgement of the physician, the potential benefits outweigh the risks. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if Morphine Sulfate Injection, USP is used in this population.

Occasionally, morphine sulfate may prolong labour through actions which temporarily reduce the strength, duration and frequency of uterine contraction. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labour.

Pediatrics (< 12 years of age): The safety and efficacy of morphine sulfate have not been studied in the pediatric population. Therefore, use of Morphine Sulfate Injection, USP is not recommended in patients under 12 years of age.

Geriatrics (> 65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION).

Patients with Hepatic or Renal Impairment:
Elimination half-life may be prolonged in patients with reduced metabolic rates and with hepatic or renal dysfunction. Therefore, care should be exercised in administering Morphine Sulfate Injection, USP in these conditions, particularly with repeated dosing.

Ambulatory Patients
Since opioid analgesics may impair the mental and/or physical abilities, patients should be warned not to drive cars, or operate machinery, or unnecessarily expose themselves to hazards.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Adverse effects of morphine sulfate are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The major hazards associated with morphine sulfate include the following: respiratory depression, apnea, and to a lesser degree, circulatory depression. Respiratory arrest, shock, and cardiac arrest have occurred.

The most frequent adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem more prominent in ambulatory patients and in those who are not suffering from severe pain. In such individuals, lower doses are advisable.

Allergies	Pruritus, urticaria, other skin rashes, edema, and (rarely) hemorrhagic urticaria. Wheal and flare over the vein with the intravenous injection may occur. Anaphylactoid reactions have been reported following intravenous administration. Thrombocytopenia has rarely been reported.
Cardiovascular System	Orthostatic hypotension, fainting, flushing, supraventricular tachycardias, atrial flutter, tachycardia, bradycardia, palpitation, syncope, circulatory depression, peripheral circulatory collapse, and cardiac arrest have occurred. Phlebitis following intravenous injection has been reported.
Central Nervous System	Euphoria, delirium, weakness, headache, sedation, drowsiness, mental clouding, dizziness, lethargy, impairment of mental and physical performance, anxiety, convulsion, coma, insomnia, agitation, tremor, uncoordinated muscle movements, confusion,

	visual disturbance, transient hallucinations, disorientation, fear, miosis, dysphoria, psychic dependence, and mood changes, and respiratory depression.
Gastrointestinal System	Dry mouth, anorexia, nausea, vomiting, increased pressure in the biliary tract, biliary tract spasm, constipation. Patients with chronic ulcerative colitis may experience increased colonic motility; toxic dilatation has been reported in patients with acute ulcerative colitis.
Genitourinary System	Ureteral spasm, spasm of vesical sphincters, urinary retention or hesitancy, oliguria, antidiuretic effect, reduced libido and/or potency have been reported.
Other	Sweating, pruritus, suppressed cough reflex.

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy

prior to initiating treatment for diarrhea.

Post-Marketing Experience

Androgen deficiency: Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

DRUG INTERACTIONS

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. 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 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment). Morphine Sulfate Injection, USP should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Drug-Drug Interactions

Morphine analgesia may be decreased when given concomitantly with phenothiazines. When such combined therapy is contemplated, the dose of one or both agents should be appropriately adjusted.

The analgesic effect of morphine sulfate is potentiated by chlorpromazine and methocarbamol.

Morphine sulfate may increase the anticoagulant activity of coumarin and other anticoagulants.

Concurrent administration of cimetidine and morphine sulfate has been reported to precipitate apnea, confusion and muscle twitching.

Morphine sulfate is incompatible with admixtures of soluble barbiturates, chlorothiazide, aminophylline, heparin, meperidine, methicillin, phenytoin, sodium bicarbonate, iodide, sulfadiazine and sulfisoxazole.

Coadministration of morphine sulfate with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see WARNINGS AND PRECAUTIONS).

Drug-Lifestyle Interactions
The concomitant use of alcohol should be avoided (see WARNINGS AND PRECAUTIONS, General).

DOSAGE AND ADMINISTRATION

Morphine Sulfate Injection, USP should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).

For acute pain, it is recommended that Morphine Sulfate Injection, USP be used for a maximum of 7 days at the lowest dose that provides adequate pain relief.

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. For the management of chronic non-cancer, non-palliative pain, it is recommended that 90 mg (90 morphine milligram equivalent) of Morphine Sulfate Injection, USP not be exceeded. Each patient should be assessed for their risk prior to prescribing Morphine Sulfate Injection, USP, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of Morphine Sulfate Injection, USP (see DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

Dosing Considerations
Morphine Sulfate Injection, USP should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see WARNINGS AND PRECAUTIONS, Peri-operative Considerations).

Morphine Sulfate Injection, USP. is not indicated for rectal administration

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression.

Recommended Dose and Dosage Adjustment
When administered intravenously, morphine sulfate should be given **very slowly**. Rapid intravenous injection increases the incidence of adverse reactions as described above. This drug should be administered intravenously only if an opioid antagonist (i.e., naloxone) is available.

When morphine sulfate is given parenterally, especially intravenously, the patient should be non-ambulatory.

Following are the equivalences of commonly used opioid analgesics (**Table 1**), and comparison of effects of strong analgesics used in the treatment of cancer pain (**Table 2**).

Opioid Rotation
Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other

factors. When switching from one opioid to another, consider reducing the calculated dose by 25-50% to minimize the risk of overdose. Subsequently, up-titrate the dose, as required, to reach the appropriate maintenance dose.

Table 1 - Opioid Analgesics: Approximate Analgesic Equivalences[1]

DRUG	Equivalent Dose (mg) [(2)] (compared to morphine 10 mg Intramuscular)		Duration of Action (Hours)
	Parenteral	Oral	
Strong Opioid Agonists:			
Morphine	10	60[3]	3 - 4
Oxycodone	15	30[4]	2 - 4
Hydromorphone	1.5	7.5	2 - 4
Anileridine	25	75	2 - 3
Levorphanol	2	4	4 - 8
Meperidine [6]	75	300	1 - 3
Oxymorphone	1.5	5 (rectal)	3 - 4
Methadone [5]	-	-	-
Heroin	5 - 8	10 - 15	3 - 4
Weak Opioid Agonists:			
Codeine	120	200	3 - 4
Propoxyphene	50	100	2 - 4
Mixed Agonist-Antagonists [7]:			
Pentazocine [6]	60	180	3 - 4
Nalbuphine	10	-	3 - 6
Butorphanol	2	-	3 - 4

Footnotes:

[1] References:

Expert Advisory Committee on the Management of Severe Chronic Pain in Cancer Patients, Health and Welfare Canada. Cancer pain: A monograph on the management of cancer pain. Ministry of Supplies and Services Canada, 1987. Cat. No. H42-2/5-1984E.

Foley KM. The treatment of cancer pain. N Engl J Med 1985;313(2):84-95.

Aronoff GM, Evans WO. Pharmacological management of chronic pain: A review. In: Aronoff GM, editor. Evaluation and treatment of chronic pain. 2nd ed. Baltimore (MD): Williams and Wilkins; 1992. p. 359-68.

Cherny NI, Portenoy RK. Practical issues in the management of cancer pain. In: Wall PD, Melzack R, editors. Textbook of pain. 3rd ed. New York: Churchill Livingstone; 1994. p. 1437-67.

[2] Most of the data were derived from single dose, acute pain studies and should be considered an approximation for selection of doses when treating chronic pain. As analgesic conversion factors are approximate and patient response may vary, dosing should be individualized according to relief of pain and side effects. Because of incomplete cross-tolerance, dose reductions of 25% to 50% of the equianalgesic dose may be appropriate in some patients when converting from one opioid to another, particularly at high doses.† Upward titration may be required to reach

appropriate maintenance doses.
[†]Levy MH. Pharmacologic treatment of cancer pain. N Engl J Med 1996;335:1124-1132**.**
[3] **For acute pain, the oral or rectal dose of morphine is six times the injectable dose. However, for chronic dosing, clinical experience indicates that this ratio is 2-3:1 (i.e., 20-30 mg of oral or rectal morphine is equivalent to 10 mg of parenteral morphine).**
[4] Based on single entity oral oxycodone in acute pain.
[5] Extremely variable equianalgesic dose. Patients should undergo individualized titration starting at an equivalent to 1/10 of the morphine dose.
[6] Not recommended for the management of chronic pain.
[7] Mixed agonist-antagonists can precipitate withdrawal in patients on pure opioid agonists.

Table 2: COMPARISON OF STRONG ANALGESICS AND STRUCTURALLY RELATED DRUGS USED IN THE TREATMENT OF CANCER PAIN [(a)] – INTRAMUSCULAR OR SUBCUTANEOUS ADMINISTRATION

Non Proprietary (Trade) Names	Dose mg Equianalgesic to 10 mg of Morphine[(b)]	Duration Compared with Morphine
Morphine Sulfate	10	Same
Papaveretum (Pantopon)	20	Same
Hydromorphone hydrochloride (Dilaudid)	1.3	Slightly shorter
Oxymorphone hydrochloride (Numorphan)	1.1	Slightly shorter
Nalbuphine hydrochloride (Nubain)	12	Same
Heroin, diamorphine hydrochloride	4-5	Slightly shorter
Levorphanol tartrate (Levo-Dromoran)	2.3	Same
Butorphanol tartrate (Stadol)	1.5 to 2.5	Same
Pentazocine lactate or hydrochloride (Talwin)	60	Shorter
Meperidine pethidine hydrochloride (Demerol)	80	Shorter
Methadone hydrochloride (Dolophine)	10	Same

(a) Beaver, W. T. Management of cancer pain with parenteral medication. JAMA 1980; 244; 2653-2657.
(b) In terms of the area under the analgesic time-effect curve.

Morphine Sulfate Injection, USP 2 mg / mL, 4 mg / mL and 10 mg / mL

Usual Adult dose: 5 mg to 20 mg by intravenous, intramuscular or subcutaneous every 4 hours. **Not for intrathecal or epidural use.**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the injection if it is darker than pale yellow or discolored in any other way, or it contains a precipitate (see WARNINGS AND PRECAUTIONS).

Use solution only if clear or pale yellow and contains no precipitate. **Do not heat-sterilize.**

Geriatrics:
Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with

other agents that can depress respiration. Morphine Sulfate Injection, USP should be initiated at a low dose and slowly titrated to effect (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Use with Non-Opioid Medications:
If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. Morphine Sulfate Injection, USP can be safely used concomitantly with usual doses of other non-opioid analgesics.

Dose Titration:
Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response.

Adjustment or Reduction of Dosage:

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including Morphine Sulfate Injection, USP. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, goosebumps, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Following successful relief of moderate to severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see WARNINGS AND PRECAUTIONS). Tapering should be individualised and carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Opioid analgesics may only be partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

Disposal

Morphine Sulfate Injection, USP should be kept in a safe place, out of the sight and reach of children before, during and after use. Morphine Sulfate Injection, USP should not be used in front of children, since they may copy these actions.

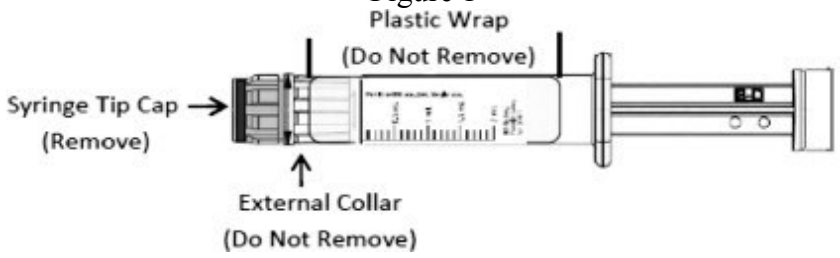
Administration

Parenteral drug products should be inspected visually for clarity of solutions, particulate matter, precipitate, discoloration, and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

Instructions for Use:

CAUTION: Certain glass syringes may malfunction, break or clog when connected to some Needleless Luer Access Devices (NLADs) and needles. This syringe has a larger internal syringe tip and an external collar (luer collar). The external collar must remain attached to the syringe. Data show that the syringe achieves acceptable connections with the BD Eclipse™ Needle and the Terumo SurGuard2™ Safety Needle and with the following non-center post NLADs: Alaris SMARTSITE™, B-Braun ULTRASITE™, BD-Q SYTE™, Maximum MAX PLUS™ and B-Braun SAFSITE™. The data also show acceptable connections are achieved to the center post ICU Medical CLAVE™. However, spontaneous disconnection of this glass syringe from needles and NLADs with leakage of drug product may occur. Assure that the needle or NLAD is securely attached before beginning the injection. Visually inspect the glass syringe-needle or glass syringe – NLAD connection before and during drug administration. Do not remove the clear plastic wrap around the external collar (see Figure 1).

Figure 1



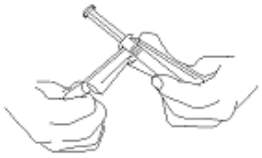
1. Inspect the outer packaging (blister pack) by verifying:
   - blister integrity
   - drug name
   - drug strength
   - dose volume
   - route of administration
   - expiration date to be sure that the drug has not expired
   - sterile field applicability

   Do not use if package has been damaged.

2. Peel open the paper (top web) of the outer packaging that displays the product information to access the syringe. Do not pop syringe through.

3. Bend the plastic part of the outer packaging (thermoform) so as to present the plunger rod for syringe removal (see Figure 2).

Figure 2

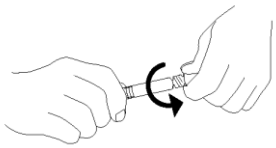


4. Perform visual inspection on the syringe by verifying
   - Absence of syringe damage
   - Absence of external particles
   - Absence of internal particles
   - Proper drug colour
   - Expiration date to be sure that the drug has not expired
   - Drug name
   - Drug strength
   - Dose volume
   - Route of administration
   - Sterile field applicability
   - Integrity of the plastic wrap around the external collar

5. Do not remove plastic wrap around the external collar. Push plunger rod slightly to break the stopper loose while tip cap is still on.

6. Do not remove plastic wrap around the external collar. Remove tip cap by twisting it off (see Figure 3).

Figure 3



7. Discard the tip cap.

8. Expel air bubble.

9. Adjust dose into sterile material (if applicable).

10. Connect the syringe to appropriate injection connection depending on route of administration. Before injection, ensure that the syringe is securely attached to the needle or needleless luer access device (NLAD).

11. Depress plunger rod to deliver medication. Ensure that pressure is maintained on the plunger rod during the entire administration.

12. Remove syringe from NLAD (if applicable) and discard into appropriate receptacle. If delivering medication via intramuscular (IM) route, do not recap needle. To prevent needle-stick injuries, needles should not be recapped.

NOTES:

- All steps must be done sequentially.
- **Do not autoclave syringe.**
- **Do not use this product on a sterile field.**
- Do not introduce any other fluid into the syringe at any time.
- This product is for single use only

Simplist is a trademark of Fresenius Kabi USA, LLC.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms:
Overdosage with morphine sulfate is characterized by respiratory depression ((a decrease in respiratory rate and/or tidal volume; Cheyne-Stokes respiration; cyanosis), pinpoint pupils, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment:
Primary attention should be given to the re-establishment of adequate respiratory exchange through the provision of a patent airway and institution of assisted or controlled ventilation. Naloxone hydrochloride is a specific and effective antagonist for respiratory depression which may result from overdosage or sensitivity to opioids. The usual initial adult dose is 0.4 mg to 2 mg naloxone administered intravenously. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately following intravenous

administration, it may be repeated intravenously at 2- or 3-minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or nonopioid drugs.

The usual initial pediatric dose is 0.01 mg/kg body weight, given intravenously, intramuscularly or subcutaneously. This dose may be repeated in accordance with the adult administration guideline. If necessary, naloxone can be diluted with Sterile Water for Injection. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Morphine is not dialyzable.

Toxic dose of morphine in humans by parenteral routes: A dose in excess of 30 mg rapidly administered is likely to induce significant toxic effects in the nonaddicted adult who is not in pain.

Note: In an individual physically dependent on opioids, the administration of the usual dose of an opioid antagonist will precipitate an acute withdrawal syndrome. 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, the antagonist should be administered with extreme care and only one-tenth to one-fifth the usual dose administered.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Morphine, an opium alkaloid, is an opiate agonist and provides analgesia at a dose that does not produce severe alterations in consciousness. Its principal therapeutic effect is relief of pain. Its exact mechanism and locus of action are not known, but are believed to relate to the existence of opiate receptors in the central nervous system. The drug affects both the initial perception of pain and the emotional response to it and although pain relief is not usually complete, the level of distress or suffering is markedly decreased. In addition to analgesia, opioids produce drowsiness, changes in mood, and mental clouding; however, neither sensory modalities nor motor activity are blocked at therapeutic doses. There is no intrinsic limit to the analgesic effect, but high dosages can produce adverse effects such as respiratory depression, nausea and vomiting, cough reflex depression, miosis, mild vasodilation and an increase in tone of the gastrointestinal and genitourinary tracts.

Pharmacodynamics

Central Nervous System:

Morphine sulfate produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO_2 tension and to electrical stimulation.

Morphine sulfate depresses the cough reflex by direct effect on the cough centre in the medulla.

Antitussive effects may occur with doses lower than those usually required for analgesia.

Morphine sulfate causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of morphine sulfate overdose.

Gastrointestinal Tract and Other Smooth Muscle: Morphine sulfate causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System:
Morphine sulfate may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

Endocrine System:
Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

Immune System:
In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Concentration – Efficacy Relationships
Pain relief generally begins within several minutes after intravenous injection. Higher doses provide greater analgesic effect and longer duration of action but adverse effects limit the maximum tolerated dose.

Pharmacokinetics
Morphine is detoxified in the liver by conjugation with glucuronic acid. Small amounts of the free drug and larger amounts of conjugated morphine are found in the urine. These account for most of the administered drug and 90% of the total excretion occurs within the first 24 hours.

Special Populations and Conditions

Pediatrics: Individuals under 12 years of age should not take Morphine Sulfate Injection, USP.

STORAGE AND STABILITY

Store at 15 °C to 30 °C. Protect from light and freezing.

Morphine Sulfate Injection, USP and dilutions of Morphine Sulfate Injection, USP in dextrose injection 5 % or sodium chloride injection 0.9% can be stored in portable infusion pump cassettes, syringes, and PVC minibags. Protected from light, they will stay stable for 24 hours at room temperature (store at 15 °C to 30 °C) or for 72 hours if kept refrigerated (store at 2 °C to 8 °C). Appropriate aseptic techniques must be used in order to minimize contamination of the solution.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Morphine Sulfate Injection, USP 2 mg / mL is available in 1 mL Simplist™ prefilled single use syringes in boxes of 24.

Each mL of Morphine Sulfate Injection, USP 2 mg / mL contains: morphine sulfate 2 mg, sodium chloride 8.4 mg, sodium citrate dihydrate 2.3 mg, citric acid monohydrate 0.74 mg, edetate disodium 0.111 mg, calcium chloride dihydrate 0.053 mg and water for injection.

Morphine Sulfate Injection, USP 4 mg / mL is available in 1 mL Simplist™ prefilled single use syringes in boxes of 24.

Each mL of Morphine Sulfate Injection, USP 4 mg / mL contains: morphine sulfate 4 mg, sodium chloride 8.4 mg, sodium citrate dihydrate 2.3 mg, citric acid monohydrate 0.74 mg, edetate disodium 0.111 mg, calcium chloride dihydrate 0.053 mg and water for injection.

Morphine Sulfate Injection, USP 10 mg / mL is available in 1 mL Simplist™ prefilled single use syringes in boxes of 24.

Each mL of Morphine Sulfate Injection, USP 10 mg / mL contains: morphine sulfate 10 mg, sodium chloride 7.5 mg, sodium citrate dihydrate 3.45 mg, citric acid monohydrate 1.11 mg, edetate disodium 0.111 mg, calcium chloride dihydrate 0.053 mg and water for injection

PART II: SCIENTIFIC INFORMATION

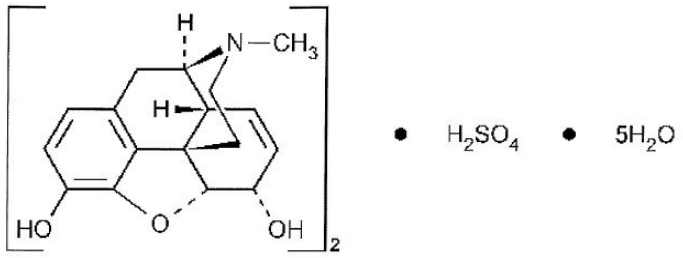
PHARMACEUTICAL INFORMATION

Drug Substance
Proper name:
Morphine sulfate pentahydrate

Chemical name:
7,-8-Didehydro-4, 5α-epoxy-17-methylmorphinan-3, 6α-diol sulfate (2:1)(salt) pentahydrate

Molecular formula and molecular mass:
Molecular formula: $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$
Molecular mass: 758.83 g/mol

Structural formula:



Physicochemical Properties:
A fine, white powder. When exposed to air it gradually loses water of hydration, and darkens on prolonged exposure to light. It is soluble in water and ethanol at room temperature.

REFERENCES

Morphine Sulfate Injection, USP. Hospira Healthcare Corporation. Product Monograph. Control Number: 211417. Date of Revision: March 9, 2018.

Morphine Sulfate Injection, SDZ. Sandoz Canada Inc. Product Monograph. Control Number: 217218. Date of Revision: August 31, 2018.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

^{N}Morphine Sulfate Injection, USP

Read this carefully before you start taking Morphine Sulfate Injection, USP. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Morphine Sulfate Injection, USP.

Serious Warnings and Precautions

- **Even if you take Morphine Sulfate Injection, USP as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **You may get life-threatening breathing problems while taking Morphine Sulfate Injection, USP. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **If a person has not been prescribed Morphine Sulfate Injection, USP taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took Morphine Sulfate Injection, USP while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
  - **has changes in their breathing (such as weak, difficult or fast breathing)**
  - **is unusually difficult to comfort**
  - **has tremors (shakiness)**
  - **has increased stools, sneezing, yawning, vomiting, or fever**

  Seek immediate medical help for your baby.
- **Taking Morphine Sulfate Injection, USP with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**

What is Morphine Sulfate Injection, USP used for?
Morphine Sulfate Injection, USP is an injection containing morphine sulfate (an opioid analgesic) used to control your pain.

How does Morphine Sulfate Injection, USP work?
Morphine Sulfate Injection, USP is a painkiller belonging to the class of drugs known as opioids.

It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in Morphine Sulfate Injection, USP?
Medicinal ingredient: Morphine sulfate
Non-medicinal ingredients: Sodium chloride, Sodium Citrate Dihydrate, Citric Acid, Edetate Disodium, Calcium Chloride Dihydrate and water for injection

Morphine Sulfate Injection, USP comes in the following dosage form:
Sterile solution for injection of 2 mg / mL, 4 mg / mL and 10 mg / mL in Simplist™ prefilled single use syringes

Do not use Morphine Sulfate Injection, USP if:

- your doctor did not prescribe it for you
- you are allergic to morphine sulfate or any of the other ingredients in Morphine Sulfate Injection, USP
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Morphine Sulfate Injection, USP. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver or lung disease
- have heart disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have problems with your thyroid, adrenal or prostate gland
- have, or had in the past hallucinations or other severe mental problems
- suffer from migraines
- are planning to become pregnant

Other warnings you should know about:

Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

Pregnancy, nursing, labour and delivery: Opioids can be transferred to your baby through breast milk, or while still in the womb. Morphine Sulfate Injection, USP can then cause life-threatening breathing problems in your unborn baby or nursing infant. Your doctor will determine if the benefits of using Morphine Sulfate Injection, USP outweigh the risks to your unborn baby or nursing infant.

If you are pregnant and are taking Morphine Sulfate Injection, USP, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your doctor will monitor and guide you on how to slowly stop taking Morphine Sulfate Injection, USP. This may help avoid serious harm to your unborn baby.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to Morphine Sulfate Injection, USP. Morphine Sulfate Injection, USP can cause:

- drowsiness
- dizziness or
- lightheadedness

This can usually occur after you take your first dose and when your dose is increased.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off Morphine Sulfate Injection, USP.

Serotonin Syndrome: Morphine Sulfate Injection, USP can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take Morphine Sulfate Injection, USP with certain anti-depressants or migraine medications.

Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Sexual Function/Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being

infertile.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Morphine Sulfate Injection, USP:

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking Morphine Sulfate Injection, USP. It can lead to:
    - drowsiness
    - unusually slow or weak breathing
    - serious side effects or
    - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by Morphine Sulfate Injection, USP
- other opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do not** take **Morphine Sulfate Injection, USP** with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

How to take Morphine Sulfate Injection, USP:

<u>Morphine Sulfate Injection, USP 2 mg / mL, 4 mg / mL and 10 mg / mL</u>
Usual Adult dose: 5 mg to 20 mg by intravenous, intramuscular or subcutaneous every 4 hours.
Not for intrathecal or epidural use.

Usual Adult Starting Dose:
Your dose is tailored/personalized just for you.

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take Morphine Sulfate Injection, USP for up to 7 days. If you need to take

Morphine Sulfate Injection, USP for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your doctor to determine if you still need Morphine Sulfate Injection, USP. Be sure to use Morphine Sulfate Injection, USP only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking Morphine Sulfate Injection, USP tell your doctor immediately.

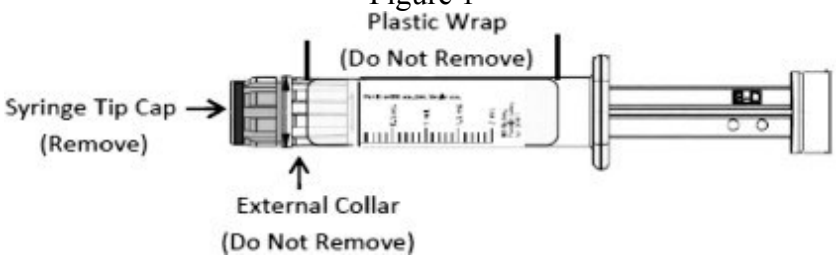
Administration

Parenteral drug products should be inspected visually for clarity of solutions, particulate matter, precipitate, discoloration, and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

Instructions for Use:

CAUTION: Certain glass syringes may malfunction, break or clog when connected to some Needleless Luer Access Devices (NLADs) and needles. This syringe has a larger internal syringe tip and an external collar (luer collar). The external collar must remain attached to the syringe. Data show that the syringe achieves acceptable connections with the BD Eclipse™ Needle and the Terumo SurGuard2™ Safety Needle and with the following non-center post NLADs: Alaris SMARTSITE™, B-Braun ULTRASITE™, BD-Q SYTE™, Maximum MAX PLUS™ and B-Braun SAFSITE™. The data also show acceptable connections are achieved to the center post ICU Medical CLAVE™. However, spontaneous disconnection of this glass syringe from needles and NLADs with leakage of drug product may occur. Assure that the needle or NLAD is securely attached before beginning the injection. Visually inspect the glass syringe-needle or glass syringe –NLAD connection before and during drug administration. Do not remove the clear plastic wrap around the external collar (see Figure 1).

Figure 1



1. Inspect the outer packaging (blister pack) by verifying:
   - blister integrity
   - drug name
   - drug strength
   - dose volume
   - route of administration

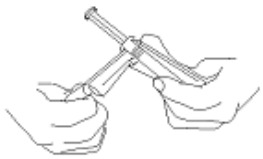
- expiration date to be sure that the drug has not expired
- sterile field applicability

Do not use if package has been damaged.

2. Peel open the paper (top web) of the outer packaging that displays the product information to access the syringe. Do not pop syringe through.

3. Bend the plastic part of the outer packaging (thermoform) so as to present the plunger rod for syringe removal (see Figure 2).

Figure 2

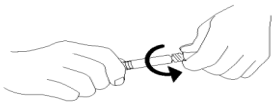


4. Perform visual inspection on the syringe by verifying
   - Absence of syringe damage
   - Absence of external particles
   - Absence of internal particles
   - Proper drug colour
   - Expiration date to be sure that the drug has not expired
   - Drug name
   - Drug strength
   - Dose volume
   - Route of administration
   - Sterile field applicability
   - Integrity of the plastic wrap around the external collar

5. Do not remove plastic wrap around the external collar. Push plunger rod slightly to break the stopper loose while tip cap is still on.

6. Do not remove plastic wrap around the external collar. Remove tip cap by twisting it off (see Figure 3).

Figure 3



7. Discard the tip cap.

8. Expel air bubble.

9. Adjust dose into sterile material (if applicable).

10. Connect the syringe to appropriate injection connection depending on route of administration. Before injection, ensure that the syringe is securely attached to the needle or needleless luer access device (NLAD).

11. Depress plunger rod to deliver medication. Ensure that pressure is maintained on the plunger rod during the entire administration.

12. Remove syringe from NLAD (if applicable) and discard into appropriate receptacle. If delivering medication via intramuscular (IM) route, do not recap needle. To prevent needle-stick injuries, needles should not be recapped.

NOTES:

- All steps must be done sequentially.
- **Do not autoclave syringe.**
- **Do not use this product on a sterile field.**
- Do not introduce any other fluid into the syringe at any time.
- This product is for single use only

Simplist is a trademark of Fresenius Kabi USA, LLC.

Stopping your Medication

If you have been taking Morphine Sulfate Injection, USP for more than a few days you should not stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking Morphine Sulfate Injection, USP. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea

- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness
- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking Morphine Sulfate Injection, USP.

Refilling your Prescription for Morphine Sulfate Injection, USP:

A new written prescription is required from your doctor each time you need more Morphine Sulfate Injection, USP.

Only obtain prescriptions for this medicine from the doctor in charge of your treatment. Do not seek prescriptions from other doctors unless you switch to another doctor for your pain management.

Overdose:

If you think you have taken too much Morphine Sulfate Injection, USP contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs of overdose may include:
- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

What are possible side effects from using Morphine Sulfate Injection, USP?
These are not all the possible side effects you may feel when taking Morphine Sulfate Injection, USP. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- Drowsiness
- Insomnia

- Dizziness
- Fainting
- Nausea, vomiting, or a poor appetite
- Dry mouth Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using Morphine Sulfate Injection, USP.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE **Overdose:** hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin.			✓
Respiratory Depression: slow, shallow or weak breathing.			✓
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			✓
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		✓	
Fast, Slow or Irregular Heartbeat: heart palpitations.		✓	
Low Blood Pressure: dizziness, fainting, light-headedness.	✓		
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- **Keep unused or expired Morphine Sulfate Injection, USP in a secure place to prevent theft, misuse or accidental exposure.**
- Store at 15 °C to 30 °C. Protect from light and freezing.
- **Keep Morphine Sulfate Injection, USP under lock, out of sight and reach of children and pets.**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes Morphine Sulfate Injection, USP, get emergency help right away.**

If you want more information about Morphine Sulfate Injection, USP:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); Fresenius Kabi Canada's website (http://www.fresenius-kabi.com/en-ca/), or by calling 1-877-821-7724.

This information is current up to the time of the date of preparation shown below, but more current information may be available from Fresenius Kabi.

This leaflet was prepared by:

Fresenius Kabi Canada Ltd.
165 Galaxy Blvd, Suite 100
Toronto, ON M9W 0C8

Date of Preparation: May 15, 2019