Morphine Sulfate Injection, USP
ONLY FOR USE WITH COMPATIBLE INTRAVENOUS INFUSION PUMPS

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF MORPHINE SULFATE INJECTION

Addiction, Abuse, and Misuse
Because the use of Morphine Sulfate Injection exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death, assess each patient's risk prior to prescribing and reassess all patients regularly for the development of these behaviors and conditions (see WARNINGS).

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Morphine Sulfate Injection, especially upon initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of Morphine Sulfate Injection are essential (see WARNINGS).

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. Reserve concomitant prescribing of Morphine Sulfate Injection and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate (see WARNINGS, DRUG INTERACTIONS).

Neonatal Opioid Withdrawal Syndrome (NOWS)
If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of NOWS, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery (see WARNINGS).

DESCRIPTION

Morphine Sulfate Injection, USP is an opioid agonist, available as a sterile, nonpyrogenic, isotonic solution of morphine sulfate, USP (pentahydrate) in a citrate buffer. This product is to be administered intravenously using a compatible infusion pump.

Each mL contains: morphine sulfate pentahydrate 1 mg or 2 mg, sodium chloride 8.5 mg with citric acid (anhydrous) 0.4 mg and sodium citrate (dihydrate) 0.2 mg added as buffers. Hydrochloric acid and/or sodium hydroxide may be added for adjustment to pH 2.5 to 6.5.

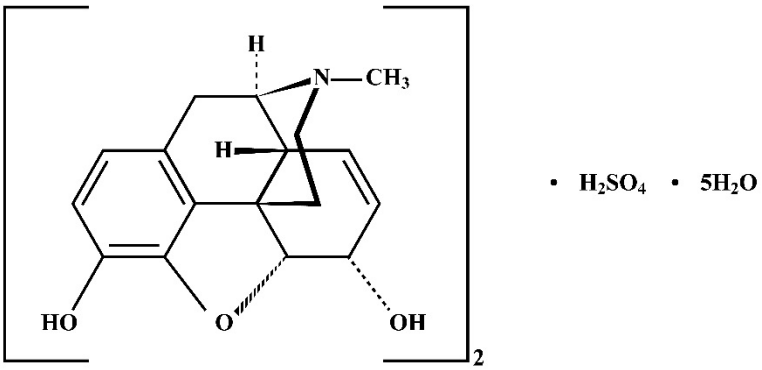
The solution contains no antioxidant, bacteriostatic or antimicrobial agents. The single-dose unit is intended to provide multiple intravenous injections only via a compatible infusion pump, either as an incremental dose or in combination with basal infusion.

THIS PRODUCT IS NOT TO BE USED FOR EPIDURAL OR INTRATHECAL INFUSIONS.

When the dosing requirement is completed, the unused portion and the syringe should be discarded in an appropriate manner.

Morphine sulfate USP is an odorless, white crystalline powder with a bitter taste. It has a solubility of 1 in 21 parts of water and 1 in 1000 parts of alcohol, but is practically insoluble in chloroform or ether. The octanol:water partition coefficient of morphine is 1.42 at physiologic pH and the pKa is 7.9 for the tertiary nitrogen (the majority is ionized at pH 7.4).

Morphine sulfate (pentahydrate) is chemically designated 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3, 6α-diol sulfate (2:1)(salt), pentahydrate, a white crystalline powder, soluble in water. It has the following chemical structure:



$[C_{15}H_{21}NO_2]_2 \cdot H_2SO_4 \cdot 5H_2O$

M.W. = 758.83

CLINICAL PHARMACOLOGY

Morphine is a full opioid agonist and is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of morphine is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with morphine. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

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

In opioid naive postoperative patients, the minimal effective concentration (MEC) calculated for a 70 kg person is 20 ng/mL, usually achieved by a dosage of approximately 2 mg/hr by patient controlled analgesia (PCA). The total daily dose requirements of postoperative narcotic can vary 10-fold in opioid **naive** surgical patients.

The usual MEC in postoperative patients given PCA is 20-40 ng/mL, and morphine is consistently effective at plasma levels over 40 ng/mL, but may be associated with respiratory depression in some patients. Opioid tolerant patients with burns and severe multiple injuries have safely tolerated much greater doses.

The elderly may have increased sensitivity to morphine and may achieve higher and more variable serum levels than younger patients. Older patients have smaller volumes of distribution; accordingly, initial concentrations of morphine can be higher.

In adults, the duration of action of morphine-induced analgesia increases progressively with age, although the degree of analgesia remains unchanged. Pediatric patients may require higher plasma levels of morphine than adults to achieve effective analgesia. Neonates, however, have reduced rates of metabolism and elimination so that dosing requirements are lower than those of older children and adults.

Pharmacodynamics

Effects on the Central Nervous System

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

Morphine 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 origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Morphine 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 biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System
Morphine produces peripheral vasodilation, which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating and/or orthostatic hypotension.

Effects on the Endocrine System
Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans (see **ADVERSE REACTIONS**). They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Use of opioids for an extended period of time 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 (see **ADVERSE REACTIONS**).

Effects on the Immune System
Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration-Efficacy Relationships
The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with opioid agonists. The minimum effective analgesic concentration of morphine for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance (see **DOSAGE AND ADMINISTRATION**).

Concentration-Adverse Reaction Relationships
There is a relationship between increasing morphine plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions (see **DOSAGE AND ADMINISTRATION**).

Pharmacokinetics

Distribution
After an IV bolus dose, the mean volume of distribution is between 3-4 L/kg. Morphine is approximately 35% protein bound, mainly to albumin.

Metabolism
The major metabolic pathway of morphine is glucuronide conjugation to generate morphlne-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), an opioid agonist. Between the two glucuronides, M3G is the major and M6G is the minor metabolite. Other

minor metabolites are codeine, normorphine and morphine etheral sulfate. Morphine is reported to undergo some degree of enterohepatic recirculation.

Elimination
Only about 10% of a morphine dose is excreted unchanged in the urine. Most of the dose is excreted in the urine as M3G and M6G. Adult plasma clearance is approximately 20-30 mL/minute/kg. The effective terminal half-life of morphine after IV administration is approximately 2 hours. Longer plasma sampling in some studies suggests a longer terminal half-life of about 15 hours.

Special Populations

Hepatic Impairment
Morphine pharmacokinetics are altered in individuals with cirrhosis. Clearance was found to decrease with a corresponding increase in half-life. The M3G and M6G to morphine plasma AUC ratios also decreased in these patients, indicating decreased metabolic activity. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted.

Renal Impairment
The pharmacokinetics of morphine are altered in patients with renal failure. The AUC is increased and clearance is decreased and the metabolites, M3G and M6G, accumulate to much higher levels in patients with renal failure as compared with patients with normal renal function. Adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been conducted.

Pediatric
Morphine glucuronidation capacity is not fully developed in the neonate. Compared to older children and adults, neonates under 1 month of age have decreased clearance and increased elimination half-life. These parameters correlate with gestational and postnatal age. Protein binding is reduced to approximately 20%.

Pregnancy
Morphine is rapidly transferred to the fetus. The rate of morphine elimination from the fetus is dictated by maternal elimination characteristics; placental clearance is the predominant route of drug elimination for the fetus.

Nursing Mothers
Morphine is excreted in the maternal milk and the milk-to-plasma morphine AUC ratio is approximately 2.5. The amount of morphine received by the nursing infant depends on the maternal plasma concentration, amount of milk consumed by the nursing infant, and the extent of first pass effect.

INDICATIONS AND USAGE

Morphine Sulfate Injection is an opioid agonist, indicated for the management of pain severe enough to require use of an opioid analgesic by intravenous Patient-Controlled

Analgesia (PCA) with a compatible PCA pump, or for controlled continuous intravenous infusion, and for which alternative treatments are inadequate.

CONTRAINDICATIONS

Morphine Sulfate Injection is contraindicated in patients with:

- Significant respiratory depression (see **WARNINGS**)
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (see **WARNINGS**)
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days (see **WARNINGS**)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (see **WARNINGS**)
- Hypersensitivity to morphine (e.g., anaphylaxis) (see **ADVERSE REACTIONS**)

WARNINGS

Addiction, Abuse, and Misuse

Morphine Sulfate Injection contains morphine, a Schedule II controlled substance. As an opioid, Morphine Sulfate Injection exposes users to the risks of addiction, abuse, and misuse (see **DRUG ABUSE AND DEPENDENCE**).

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Morphine Sulfate Injection. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing Morphine Sulfate Injection, and monitor all patients receiving Morphine Sulfate Injection for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as Morphine Sulfate Injection but use in such patients necessitates intensive counseling about the risks and proper use of Morphine Sulfate Injection along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing Morphine Sulfate Injection. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity.

Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Life-Threatening Respiratory Depression

Serious, life-threating, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, 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 (see **OVERDOSAGE**). Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Morphine Sulfate Injection, the risk is greatest during the initiation of therapy or following a dosage increase. Because of a delay in the maximum CNS effect with intravenously administered Morphine Sulfate Injection (30 min), rapid administration may result in overdosing. The respiratory depression may be severe and could require intervention.

To reduce the risk of respiratory depression, proper dosing and titration of Morphine Sulfate Injection are essential (see **DOSAGE AND ADMINISTRATION**). Overestimating the Morphine Sulfate Injection dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper (see **DOSAGE AND ADMINISTRATION**).

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Morphine Sulfate Injection with benzodiazepines and/or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Monitor patients closely for signs of respiratory depression and sedation.

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.

Neonatal Opioid Withdrawal Syndrome

Use of Morphine Sulfate Injection for an extended period of time during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (see **PRECAUTIONS, Information for Patients/Caregivers, Pregnancy**).

Opioid-Induced Hyperalgesia and Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect (see Dependence). Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation (safely switching the patient to a different opioid moiety) (see **WARNINGS, DOSAGE AND ADMINISTRATION**).

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.

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.

Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of Morphine Sulfate Injection in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease
Morphine Sulfate Injection-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of Morphine Sulfate Injection (see **WARNINGS**).

Elderly, Cachectic, or Debilitated Patients
Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients (see **WARNINGS**).

Monitor such patients closely, particularly when initiating and titrating Morphine Sulfate Injection and when Morphine Sulfate Injection is given concomitantly with other drugs that depress respiration (see **WARNINGS**). Alternatively, consider the use of non-opioid analgesics in these patients.

Interaction with Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) may potentiate the effects of morphine, including respiratory depression, coma, and confusion. Morphine Sulfate Injection should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than 1 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.

Severe Hypotension

Morphine Sulfate Injection may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g.,

phenothiazines or general anesthetics) (see **Drug Interactions**). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Morphine Sulfate Injection. In patients with circulatory shock, Morphine Sulfate Injection may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Morphine Sulfate Injection in patients with circulatory shock.

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), Morphine Sulfate Injection may reduce the respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Morphine Sulfate Injection.

Opioids may obscure the clinical course in a patient with a head injury. Avoid the use of Morphine Sulfate Injection in patients with impaired consciousness or coma.

Risks of Use in Patients with Gastrointestinal Conditions

Morphine Sulfate Injection is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The morphine in Morphine Sulfate Injection may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

Risk of Seizures

The morphine in Morphine Sulfate Injection may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Morphine Sulfate Injection therapy.

Excitation of the central nervous system, resulting in convulsions, may accompany high doses of morphine given intravenously.

Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including Morphine Sulfate Injection. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms.

When discontinuing Morphine Sulfate Injection, gradually taper the dosage (see **DOSAGE AND ADMINISTRATION**). Do not abruptly discontinue Morphine Sulfate Injection (see **DRUG ABUSE AND DEPENDENCE**).

Risk of Driving and Operating Machinery

Morphine Sulfate Injection may impair the mental or physical abilities needed to perform potentially hazardous activities, such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Morphine Sulfate Injection and know how they will react to the medication (see **PRECAUTIONS, Information for Patients/Caregivers).**

PRECAUTIONS

Do not use unless solution is clear and package is undamaged (see **DOSAGE AND ADMINISTRATION**).

Parenteral Therapy

Give by slow intravenous (IV) injection. Rapid IV injection of morphine and other narcotic analgesics increases the incidence of adverse reactions. Severe respiratory depression, hypotension, apnea, peripheral circulatory collapse, cardiac arrest and anaphylactic reactions have occurred. When given parenterally, especially IV, patients should be lying down when therapy is initiated, and care should be used when getting them up to prevent syncope.

Pediatric Use

Morphine Sulfate Injection should be administered to opioid-naive pediatric patients only in settings in which respiratory function is monitored and there is immediate access to age-appropriate life support equipment and personnel skilled in management of respiratory and cardiovascular depression in pediatric patients.

Renal and Hepatic Dysfunction

Morphine may have a prolonged duration and cumulative effect in patients with renal or hepatic dysfunction.

Information for Patients/Caregivers

Addiction, Abuse, and Misuse

Inform patients that the use of Morphine Sulfate Injection, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death (see **WARNINGS**).

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting Morphine Sulfate Injection or when the dosage is increased, and that it can occur even at recommended dosages (see **WARNINGS**).

Hyperalgesia and Allodynia

Advise patients to inform their healthcare professional if they experience symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain (see **WARNINGS, ADVERSE REACTIONS**).

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition called serotonin syndrome resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking or plan to take serotonergic medications (see **PRECAUTIONS, Drug Interactions**).

Constipation

Advise patients of the potential for severe constipation (see **ADVERSE REACTIONS, CLINICAL PHARMACOLOGY**).

Drug Interactions

Benzodiazepines and Other Central Nervous System (CNS) Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol (e.g., other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids), 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. Monitor closely for signs of respiratory depression and sedation (see **WARNINGS**).

Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue), has resulted in serotonin syndrome (see **PRECAUTIONS, Information for Patients/Caregivers** and **ADVERSE REACTIONS**).

If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Morphine Sulfate Injection if serotonin syndrome is suspected.

Monoamine Oxidase Inhibitors (MAOIs)

MAOI (such as phenelzine, tranylcypromine, linezolid) interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma).

Do not use Morphine Sulfate Injection in patients taking MAOIs or within 14 days of stopping such treatment.

If urgent use of an opioid is necessary, use test doses and frequent titration of small doses of other opioids (such as oxycodone, hydrocodone, oxymorphone, hydrocodone, or buprenorphine) to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics
Mixed agonist/antagonist analgesics (e.g., butorphanol, nalbuphine, pentazocine, buprenorphine) may reduce the analgesic effect of Morphine Sulfate Injection and/or precipitate withdrawal symptoms. Avoid concomitant use.

Muscle Relaxants
Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Morphine Sulfate Injection and/or the muscle relaxant as necessary.

Diuretics
Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

Anticholinergic Drugs
The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when Morphine Sulfate Injection is used concomitantly with anticholinergic drugs.

Cimetidine

The concomitant administration of morphine sulfate and cimetidine has been reported to precipitate apnea, confusion and muscle twitching in an isolated report.

Monitor patients for increased respiratory and CNS depression when receiving cimetidine concomitantly with Morphine Sulfate Injection.

Oral $P2Y_{12}$ Inhibitors

The co-administration of oral $P2Y_{12}$ inhibitors (e.g., clopidogrel, prasugrel, ticagrelor) and intravenous morphine sulfate can decrease the absorption and peak concentration of oral $P2Y_{12}$ inhibitors and delay the onset of the antiplatelet effect.

Consider the use of a parenteral antiplatelet agent in the setting of acute coronary syndrome requiring co-administration of intravenous morphine sulfate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of morphine have not been conducted.

Mutagenesis

No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic *in vitro* increasing DNA fragmentation in human T-cells. Morphine was reported to be mutagenic in the *in vivo* mouse micronucleus assay and positive for the induction of chromosomal aberrations in mouse spermatids and murine lymphocytes. Mechanistic studies suggest that the *in vivo* clastogenic effects reported with morphine in mice may be related to increases in glucocorticoid levels produced by morphine in this species. In contrast to the above positive findings, *in vitro* studies in the literature have also shown that morphine did not induce chromosomal aberrations in human leukocytes or translocations or lethal mutations in Drosophila.

Impairment of Fertility

No formal nonclinical studies to assess the potential of morphine to impair fertility have been conducted.

Several nonclinical studies from the literature have demonstrated adverse effects on male fertility in the rat from exposure to morphine. One study in which male rats were administered morphine sulfate subcutaneously prior to mating (up to 30 mg/kg twice daily) and during mating (20 mg/kg twice daily) with untreated females, a number of adverse reproductive effects including reduction in total pregnancies and higher incidence of pseudopregnancies at 20 mg/kg/day (3.2 times the HDD) were reported.

Studies from the literature have also reported changes in hormonal levels in male rats (i.e., testosterone, luteinizing hormone) following treatment with morphine at 10 mg/kg/day or greater (1.6 times the HDD).

Female rats that were administered morphine sulfate intraperitoneally prior to mating exhibited prolonged estrous cycles at 10 mg/kg/day (1.6 times the HDD).

Exposure of adolescent male rats to morphine has been associated with delayed sexual maturation and following mating to untreated females, smaller litters, increased pup mortality, and/or changes in reproductive endocrine status in adult male offspring have been reported (estimated 5 times the plasma levels at the HDD).

Pregnancy

Risk Summary

Use of opioid analgesics for an extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome (see **WARNINGS**). There are no available data with Morphine Sulfate Injection in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. Published studies with morphine use during pregnancy

have not reported a clear association with morphine and major birth defects (see *Human Data*).

In published animal reproduction studies, morphine administered subcutaneously during the early gestational period produced neural tube defects (i.e., exencephaly and cranioschisis) at 5 and 16 times the human daily dose of 60 mg based on body surface area (HDD) in hamsters and mice, respectively, lower fetal body weight and increased incidence of abortion at 0.4 times the HDD in the rabbit, growth retardation at 6 times the HDD in the rat, and axial skeletal fusion and cryptorchidism at 16 times the HDD in the mouse. Administration of morphine sulfate to pregnant rats during organogenesis and through lactation resulted in cyanosis, hypothermia, decreased brain weights, pup mortality, decreased pup body weights, and adverse effects on reproductive tissues at 3-4 times the HDD; and long-term neurochemical changes in the brain of offspring which correlate with altered behavioral responses that persist through adulthood at exposures comparable to and less than the HDD (see *Animal Data*). Based on animal data, advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions
Use of opioid analgesics for an extended period of time during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly (see **WARNINGS**).

Labor or Delivery
Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid induced respiratory depression in the neonate. Morphine Sulfate Injection is not recommended for use in women during and immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including Morphine Sulfate Injection, can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased

rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Human Data
The results from a population-based prospective cohort, including 70 women exposed to morphine during the first trimester of pregnancy and 448 women exposed to morphine at any time during pregnancy, indicate no increased risk for congenital malformations. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design.

Animal Data
Formal reproductive and developmental toxicology studies for morphine have not been conducted. Exposure margins for the following published study reports are based on human daily dose of 60 mg morphine using a body surface area comparison (HDD).

Neural tube defects (exencephaly and cranioschisis) were noted following subcutaneous administration of morphine sulfate (35-322 mg/kg) on Gestation Day 8 to pregnant hamsters (4.7 to 43.5 times the HDD). A no adverse effect level was not defined in this study and the findings cannot be clearly attributed to maternal toxicity. Neural tube defects (exencephaly), axial skeletal fusions, and cryptorchidism were reported following a single subcutaneous (SC) injection of morphine sulfate to pregnant mice (100-500 mg/kg) on Gestation Day 8 or 9 at 200 mg/kg or greater (16 times the HDD) and fetal resorption at 400 mg/kg or higher (32 times the HDD). No adverse effects were noted following 100 mg/kg morphine in this model (8 times the HDD). In one study, following continuous subcutaneous infusion of doses greater than or equal to 2.72 mg/kg to mice (0.2 times the HDD), exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted. The effects were reduced with increasing daily dose; possibly due to rapid induction of tolerance under these infusion conditions. The clinical significance of this report is not clear.

Decreased fetal weights were observed in pregnant rats treated with 20 mg/kg/day morphine sulfate (3.2 times the HDD) from Gestation Day 7 to 9. There was no evidence of malformations despite maternal toxicity (10% mortality). In a second rat study, decreased fetal weight and increased incidences of growth retardation were noted at 35 mg/kg/day (5.7 times the HDD) and there was a reduced number of fetuses at 70 mg/kg/day (11.4 times the HDD) when pregnant rats were treated with 10, 35, or 70 mg/kg/day morphine sulfate via continuous infusion from Gestation Day 5 to 20. There was no evidence of fetal malformations or maternal toxicity.

An increased incidence of abortion was noted in a study in which pregnant rabbits were treated with 2.5 (0.8 times the HDD) to 10 mg/kg morphine sulfate via subcutaneous injection from Gestation Day 6 to 10. In a second study, decreased fetal body weights were reported following treatment of pregnant rabbits with increasing doses of morphine (10-50 mg/kg/day) during the pre-mating period and 50 mg/kg/day (16 times the HDD)

throughout the gestation period. No overt malformations were reported in either publication, although only limited endpoints were evaluated.

In published studies in rats, exposure to morphine during gestation and/or lactation periods is associated with: decreased pup viability at 12.5 mg/kg/day or greater (2 times the HDD); decreased pup body weights at 15 mg/kg/day or greater (2.4 times the HDD); decreased litter size, decreased absolute brain and cerebellar weights, cyanosis, and hypothermia at 20 mg/kg/day (3.2 times the HDD); alteration of behavioral responses (play, social-interaction) at 1 mg/kg/day or greater (0.2 times the HDD); alteration of maternal behaviors (e.g., decreased nursing and pup retrievals) in mice at 1 mg/kg or higher (0.08 times the HDD) and rats at 1.5 mg/kg/day or higher (0.2 times the HDD); and a host of behavioral abnormalities in the offspring of rats, including altered responsiveness to opioids at 4 mg/kg/day (0.7 times the HDD) or greater.

Fetal and/or postnatal exposure to morphine in mice and rats has been shown to result in morphological changes in fetal and neonatal brain and neuronal cell loss, alteration of a number of neurotransmitter and neuromodulator systems, including opioid and non-opioid systems, and impairment in various learning and memory tests that appear to persist into adulthood. These studies were conducted with morphine treatment usually in the range of 4 to 20 mg/kg/day (0.7 to 3.2 times the HDD).

Additionally, delayed sexual maturation and decreased sexual behaviors in female offspring at 20 mg/kg/day (3.2 times the HDD), and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed at 20 mg/kg/day (3.2 times the HDD). Decreased litter size and viability were observed in the offspring of male rats that were intraperitoneally administered morphine sulfate for 1 day prior to mating at 25 mg/kg/day (4.1 times the HDD) and mated to untreated females. Decreased viability and body weight and/or movement deficits in both first and second generation offspring were reported when male mice were treated for 5 days with escalating doses of 120 to 240 mg/kg/day morphine sulfate (9.7 to 19.5 times the HDD) or when female mice treated with escalating doses of 60 to 240 mg/kg/day (4.9 to 19.5 times the HDD) followed by a 5-day treatment-free recovery period prior to mating. Similar multigenerational findings were also seen in female rats pre-gestationally treated with escalating doses of 10 to 22 mg/kg/day morphine (1.6 to 3.6 times the HDD).

Lactation

Risk Summary

Morphine is present in breast milk. Published lactation studies report variable concentrations of morphine in breast milk with administration of immediate-release morphine to nursing mothers in the early postpartum period with a milk-to-plasma morphine AUC ratio of 2.5:1 measured in one lactation study. However, there is insufficient information to determine the effects of morphine on the breastfed infant and the effects of morphine on milk production. Lactation studies have not been conducted

with Morphine Sulfate Injection and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Morphine Sulfate Injection and any potential adverse effects on the breastfed infant from Morphine Sulfate Injection or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to Morphine Sulfate Injection through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of morphine is stopped or when breastfeeding is stopped.

Females and Males of Reproductive Potential

Infertility

Use of opioids for an extended period of time may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible (see **ADVERSE REACTIONS**).

In published animal studies, morphine administration adversely effected fertility and reproductive endpoints in male rats and prolonged estrus cycle in female rats (see **Carcinogenesis, Mutagenesis, Impairment of Fertility**).

Pediatric Use

There is extensive clinical experience with use of morphine in all age groups. This formulation has not been studied in pediatric patients. Injectable morphine has been used safely and effectively for patient-controlled analgesia (PCA) with a special PCA infusion device in pediatric patients 6-15 years of age. Administration of continuous intravenous infusions of morphine at full analgesic doses (not low dose background infusions for PCA) to opioid naive pediatric patients should be limited to highly monitored (intensive or intermediate care) settings. This product is not recommended for use in small infants and children due to the large amount of morphine (60-120 mg) contained in the pre-filled syringe relative to the dosing requirement of the patient.

Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to morphine sulfate. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of morphine sulfate slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression (see **WARNINGS**).

Morphine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Hepatic Impairment

Morphine sulfate pharmacokinetics have been reported to be significantly altered in patients with cirrhosis. Start these patients with a lower than normal dosage of Morphine Injection and titrate slowly while monitoring for signs of respiratory depression, sedation, and hypotension (see **CLINICAL PHARMACOLOGY**).

Renal Impairment

Morphine sulfate pharmacokinetics are altered in patients with renal failure. Start these patients with a lower than normal dosage of Morphine Injection and titrate slowly while monitoring for signs of respiratory depression, sedation, and hypotension (see **CLINICAL PHARMACOLOGY**).

ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse (see **WARNINGS**)
- Life-Threatening Respiratory Depression (see **WARNINGS**)
- Interactions with Benzodiazepines or Other CNS Depressants (see **WARNINGS**)
- Neonatal Opioid Withdrawal Syndrome (see **WARNINGS**)
- Opioid-Induced Hyperalgesia and Allodynia
- Cardiovascular Instability (see **WARNINGS**)
- Adrenal Insufficiency (see **WARNINGS**)
- Severe Hypotension (see **WARNINGS**)
- Gastrointestinal Adverse Reactions (see **WARNINGS**)
- Seizures (see **WARNINGS**)
- Withdrawal (see **WARNINGS**)

The following adverse reactions associated with the use of morphine were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The major adverse reactions associated with morphine therapy included 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.

Other adverse reactions included:

Cardiac disorders: tachycardia, bradycardia, palpitation

Eye disorders: miosis, visual impairment

Gastrointestinal disorders: dry mouth, constipation. Patients with chronic ulcerative colitis may experience increased colonic motility, toxic dilatation of the intestine or megacolon has been reported in patients with acute ulcerative colitis.

General disorders and administration site conditions: asthenia, edema, injection site erythema

Hepatobiliary disorders: biliary colic

Immune system disorders: anaphylactic reaction

Metabolism and nutritional disorders: decreased appetite

Nervous system disorders: weakness, headache, somnolence, drowsiness, pinpoint pupils, coma, insomnia, agitation, tremor, uncoordinated muscle movements, impairment of mental and physical performance, mental clouding, lethargy, fear, disorientation, confusion

Psychiatric disorders: anxiety, fear, drug dependence, mood altered euphoria, dysphoria, transient hallucinations, delirium

Renal and urinary disorders: ureteral spasm, spasm of vesicular sphincter, urinary retention, urinary hesitation, oliguria, antidiuretic effect

Reproductive system and breast disorders: erectile dysfunction, decreased libido

Skin and subcutaneous tissue disorders: pruritus, hemorrhagic urticaria, rash

Social circumstances: physical disability

Vascular disorders: flushing of face, peripheral circulatory failure, hypotension, phlebitis

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs (see **PRECAUTIONS, Information for Patients/Caregivers** and **Drug Interactions**).

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use (see **WARNINGS**).

Anaphylaxis: Anaphylactic reaction has been reported with ingredients contained in Morphine Sulfate Injection (see **CONTRAINDICATIONS**).

Androgen deficiency: Cases of androgen deficiency have occurred with use of opioids for an extended period of time (see **CLINICAL PHARMACOLOGY**).

Hyperalgesia and Allodynia: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration (see **WARNINGS**).

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Morphine Sulfate Injection contains morphine, a Schedule II controlled substance.

Abuse

Morphine Sulfate Injection contains morphine, a substance with a high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction (see **WARNINGS**).

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of Morphine Sulfate Injection increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of Morphine Sulfate Injection with alcohol and/or other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of Morphine Sulfate Injection abuse include those with a history of prolonged use of any opioid, including products containing morphine, those with a history of drug or alcohol abuse, or those who use Morphine Sulfate Injection in combination with other abused drugs.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among people who abuse drugs and people with substance use disorder. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

Morphine Sulfate Injection, like other opioids, can be diverted for nonmedical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of Morphine Sulfate Injection

Abuse of Morphine Sulfate Injection poses a risk of overdose and death. The risk is increased with concurrent use of Morphine Sulfate Injection with alcohol and/or other CNS depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Dependence

Both tolerance and physical dependence can develop during use of opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued use.

Morphine Sulfate Injection should not be abruptly discontinued in a physically-dependent patient (see **DOSAGE AND ADMINISTRATION**). If Morphine Sulfate Injection is abruptly

discontinued in a physically-dependent patient, a withdrawal syndrome may occur, typically characterized by restlessness, lacrimation, rhinorrhea, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs (see **PRECAUTIONS**).

OVERDOSAGE

Clinical Presentation

Acute overdose with morphine can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, hypoglycemia, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations (see **CLINICAL PHARMACOLOGY**).

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support measures.

Opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to morphine overdose, administer an opioid antagonist.

Because the duration of opioid reversal is expected to be less than the duration of action of morphine in Morphine Sulfate Injection, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information. Morphine is not dialyzable.

A dose in excess of 30 mg rapidly administered (or 10 mg in the elderly and high risk populations) is likely to induce significant toxic effects in the nontolerant, opioid naive adult who is not in pain.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the

antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

LONG-TERM USE

Some patients may use morphine via the intravenous route with a PCA pump for more than a few days (e.g., cancer pain patients). In these individuals, it is useful to anticipate and manage certain common events.

These events are dose dependent, and their frequency depends on the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. The most frequent of these include drowsiness, dizziness, constipation, and nausea. In many cases, the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large rapid swings in plasma concentrations of the opioid. Many of these adverse events will cease or decrease as therapy is continued and some degree of tolerance is developed, but others may be expected to remain troublesome throughout therapy.

Management of Excessive Drowsiness

Most patients receiving morphine will experience initial drowsiness. This usually disappears within 3-5 days and is not a cause of concern unless it is excessive, or accompanied by unsteadiness or confusion. Dizziness and unsteadiness may be associated with postural hypotension, particularly in elderly or debilitated patients, and has been associated with syncope and falls in non-tolerant patients started on opioids.

Excessive or persistent sedation should be investigated. Factors to be considered should include: concurrent sedative medications, the presence of hepatic or renal insufficiency, hypoxia or hypercapnia due to exacerbated respiratory failure, intolerance to the dose used (especially in older patients), disease severity and the patient's general condition.

The dosage should be adjusted according to individual needs, but additional care should be used in the selection of initial doses for the elderly patient, or in patients not already familiar with opioid analgesic medications, to prevent excessive sedation at the onset of treatment.

Management of Nausea and Vomiting

Nausea and vomiting are common after single doses of morphine or as an early undesirable effect of chronic opioid therapy. The prescription of a suitable antiemetic should be considered, with the awareness that sedation may result (see **DRUG INTERACTIONS**). 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.

Management of Constipation

Virtually all patients suffer from constipation while taking opioids on a chronic basis. Some patients, particularly elderly, debilitated or bedridden patients may become impacted. Tolerance does not usually develop for the constipating effects of opioids. Patients must be cautioned accordingly and laxatives, softeners and other appropriate treatments should be used prophylactically from the beginning of opioid therapy.

DOSAGE AND ADMINISTRATION

Important Dosage and Administration Instructions

For use with compatible intravenous infusion pumps only. Physicians should completely familiarize themselves with the infusion pump before prescribing morphine sulfate injection.

When administered intravenously, morphine sulfate should be given very slowly. Rapid intravenous injection increases the incidence of adverse reactions as described above. Intravenous morphine, even when given by PCA, poses an inescapable risk of respiratory depression. Patients should be started on IV morphine in a setting where assisted ventilation and narcotic antagonist (e.g., naloxone) are available. Patients should use caution or have assistance with ambulation.

For patient-controlled analgesia (PCA), dosage should be adjusted according to the severity of the pain and the response of the patient. There can be considerate variability in both the dosage requirement and patient response, especially between patients chronically exposed to opioid medications and those who are opioid naive.

The product is available in two strengths, morphine sulfate 1 mg/mL and 2 mg/mL contained in presterilized 60 mL syringes. This formulation can be administered as an intravenous bolus, continuous infusion or as incremental bolus doses delivered by a PCA device. Care should be taken not to confuse the two strengths, which might result in an unintentional overdose.

- Morphine Sulfate Injection should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks.

- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals (see **WARNINGS**). Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of Morphine Sulfate Injection for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.

- Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of

an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available.

- There is variability in the opioid analgesic dose and duration needed to adequately manage pain due both to the cause of pain and to individual patient factors. Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse (see **WARNINGS**).

- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with Morphine Sulfate Injection. Consider this risk when selecting an initial dose and when making dose adjustments (see **WARNINGS**).

Adult

Though dosage should be adjusted according to the severity of the pain and the response of the patient, the usual adult PCA dose is 1 mg to 5 mg per incremental bolus dose. PCA device programmed lockout times typically range from 5 to 15 minutes. Adult dosages reported in the literature have included the addition of a background continuous morphine infusion to the incremental bolus doses administered by the PCA device. PCA background continuous infusions of greater than 1 mg per hour were associated with an increased risk of adverse events without identified associated analgesic benefit.

Pediatric Patients

Dosage should be adjusted according to the severity of the pain and patient response. Starting doses should be reduced for patients with coexisting medical conditions or concomitant medications that depress respiratory or cardiovascular function.

Initial Dosage

Adequate analgesia should be established prior to initiation of PCA or maintenance continuous infusions. This can be achieved with slow bolus doses of 0.1 mg/kg repeated every 10-15 minutes until either adequate analgesia or limiting side effects appear.

Guidelines for starting doses:

PCA:	bolus	20-25 µg/kg
	lockout period	8-10 minutes
	dose limit	0.1-0.15 mg/kg/hr

Background (low dose) continuous infusion of morphine during PCA has been associated with increased incidence of adverse events.

Use of PCA in young pediatric patients is limited by the child's ability to understand and carry out the procedure.

Continuous Infusion (full analgesic dose)

For severe pain, a continuous infusion may be initiated at 0.1-0.15 mg/kg/hr. For opioid naive patients, this therapy should be limited to highly monitored (intensive or intermediate care) settings.

This product is not recommended for use in small infants and children due to the large amount of morphine (60-120 mg) contained in the pre-filled syringe relative to the dosing requirement of the patient.

Titration and Maintenance of Therapy

Individually titrate Morphine Sulfate Injection to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving Morphine Sulfate Injection to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and other of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse (see **WARNINGS**).

If after increasing the dosage, unacceptable opioid-related adverse reactions are observed (including an increase in pain after dosage increase), consider reducing the dosage (see **WARNINGS**). Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

Discontinuation of Morphine Sulfate Injection

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking Morphine Sulfate Injection, there are a variety of factors that should be considered, including the total daily dose of opioid (including Morphine Sulfate Injection) the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient.

When a patient who has been taking Morphine Sulfate Injection regularly and may be physically dependent no longer requires therapy with Morphine Sulfate Injection, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue Morphine Sulfate Injection in a physically dependent patient (see **WARNINGS** and **DRUG ABUSE AND DEPENDENCE**).

Safety and Handling Instructions

Accidental dermal exposure should be treated by the removal of any contaminated clothing and rinsing the affected area with water.

Each syringe contains a potent narcotic which has been associated with abuse and dependence among health care providers. Due to the limited indications for this product, the risk of overdosage and the risk of its diversion and abuse, it is recommended that appropriate measures be taken to control this product within the hospital or clinic.

Morphine Sulfate Injection should be subject to rigid accounting, rigorous control of wastage and restricted access.

Incompatibility

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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Morphine sulfate solutions may darken with age. Do not use if solution is darker than pale yellow, discolored in any other way or contains a precipitate. Do not use unless solution is clear and package is undamaged.

HOW SUPPLIED

Morphine Sulfate Injection, USP, 1 mg/mL and 2 mg/mL, is supplied in 60 mL unit-use syringe packages for single dose administration in a carton of ten syringes:

Concentration	Size	Code	NDC
1 mg/mL	60 mL	2L3004	0338-2686-76
2 mg/mL	60 mL	2L3005	0338-2687-76

This injector unit is for insertion into a compatible infusion device only. Remove cover from male Luer. Attach to PCA set. To load syringe injector assembly into infusion device, refer to operating manual of infusion device. See instructions for syringe inspection and assembly.

USE ASEPTIC TECHNIQUE
Do not assemble until ready to use.
Store at controlled room temperature 15° to 30°C (59° to 86°F).
Protect from light. Protect from freezing.

This Product Contains Dry Natural Rubber.

Caution: Federal (USA) law prohibits dispensing without prescription.

Manufactured by:
Mallinckrodt Inc.
St. Louis, MO 63134 USA

Rev 12/2023

Mallinckrodt™ Pharmaceuticals