HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MORPHINE SULFATE INJECTION safely and effectively. See full prescribing information for use of MORPHINE SULFATE INJECTION.

MORPHINE SULFATE injection, for intravenous or intramuscular use, CII

Initial U.S. Approval: 1941

---------- INDICATIONS AND USAGE ----------

Morphine Sulfate Injection is an opioid agonist indicated for the management of pain not responsive to non-narcotic analgesics. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Direct intravenous injection: The usual starting dose in adults is 0.1 mg to 0.2 mg per kg every 4 hours as needed for pain management. The dose should be adjusted according to the severity of pain, the occurrence of adverse events, as well as the patient's underlying disease, age and size. (2.2, 2.3)
- For IM morphine the dose should be a fixed dose of 10 mg, which will generally provide adequate analgesia for a 70 kg adult. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------

Injection, 2 mg/mL, 4 mg/mL, 5 mg/mL, 8 mg/mL and 10 mg/mL in a prefilled disposable syringe for IV or IM use. (3)

---------- CONTRAINDICATIONS ----------

- Know hypersensitivity or allergy to morphine. (4)
- Bronchial asthma or upper airway obstruction. (4)
- Respiratory depression in the absence of resuscitative equipment. (4)
- Paralytic ileus. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Dosing errors: Take care when prescribing and administering to avoid dosing errors due to confusion between different concentrations and between mg and mL, which could result in accidental overdose and death. (5.1)
- Cardiovascular instability: High doses are excitatory, resulting from sympathetic hyperactivity and increase in circulatory catecholamine. (5.2)
- Respiratory depression: Rapid intravenous administration may result in chest wall rigidity. (5.3)
- CNS toxicity: High doses are excitatory, resulting in convulsions. (5.4)
- CNS Depressants: May increase the risk of respiratory depression, hypotension, sedation, coma, or death if used in conjunction with other CNS active drugs. (5.6)
- Increased intracranial pressure of head injury: May increase respiratory depressant effects and elevate cerebrospinal fluid pressure. (5.7)
- Hypotensive effect: May cause hypotension in ambulatory patients. (5.8)
- Gastrointestinal effects: May diminish propulsive peristaltic waves in the gastrointestinal tract and prolong obstruction. (5.10)
- Biliary surgery or disorders of biliary tract: May cause spasm of the sphincter of Oddi and diminish biliary and pancreatic secretions. (5.11)

---------- ADVERSE REACTIONS ----------

The most serious adverse reactions encountered are respiratory depression, apnea, circulatory depression, respiratory arrest, shock and cardiac arrest. Other common frequently observed adverse reactions include: sedation, lightheadedness, dizziness, nausea, vomiting, constipation and diaphoresis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- DRUG INTERACTIONS ----------

- CNS depressants: Increased risk of respiratory depression. (7.1)
- Muscle relaxants: May enhance the neuromuscular blocking action of skeletal muscle relaxants and produce respiratory depression. (7.2)
- Mixed agonist/antagonist opioid analgesics: May reduce the analgesic effect and/or may precipitate withdrawal symptoms. (7.3)
- Cimetidine: May increase respiratory and CNS depression. (7.4)
- Anticholinergics: May increase the risk of urinary retention, severe constipation, or paralytic ileus. (7.6)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Pediatric patients: Safety and effectiveness and the pharmacokinetics of Morphine Sulfate Injection in pediatric patients below the age of 18 have not been established. (8.4)
- Geriatric patients: Use caution during dose selection, starting at the low end of the dosing range while carefully monitoring for side effects. (8.5)
- Renal and hepatic management: Start patients at lower doses and titrate cautiously. (8.7, 8.8)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2016

FULL PRESCRIBING INFORMATION: CONTENTS *

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Morphine sulfate is an opioid agonist indicated for the management of pain not responsive to non-narcotic analgesics.

2 DOSAGE AND ADMINISTRATION

Morphine Sulfate Injection is intended for intravenous and intramuscular administration.

2.1 General Dosing Considerations

Avoid Medication Errors

Morphine Sulfate Injection is available in five concentrations for direct injection. Take care when prescribing and administering Morphine Sulfate Injection to avoid dosing errors due to confusion between different concentrations and between mg and mL, which could result in accidental overdose and death. Ensure the proper dose is communicated and dispensed. When writing prescriptions, include both the total dose in mg and total dose in volume. Administration of Morphine Sulfate Injection should be limited to use by those familiar with the management of respiratory depression. Morphine must be injected slowly; rapid intravenous administration may result in chest wall rigidity.

Selection of patients for treatment with morphine sulfate should be governed by the same principles that apply to the use of similar opioid analgesics. Individualize treatment in every case, using non-opioid analgesics, opioids on an as needed basis and/or combination products, and chronic opioid therapy in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality, and the American Pain Society.

2.2 Individualization of Dosage

Adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of Morphine Sulfate Injection, USP, give attention to the following:

- the total daily dose, potency and specific characteristics of the opioid the patient has been taking previously;
- the reliability of the relative potency estimate used to calculate the equivalent Morphine Sulfate Injection, USP dose needed;
- the patient's degree of opioid tolerance;
- the general condition and medical status of the patient;
- concurrent medications;
- the type and severity of the patient's pain;
- risk factors for abuse, addiction or diversion, including a prior history of abuse, addiction.

The following dosing recommendation, therefore, can only be considered suggested approaches to what is actually a series of clinical decisions over time in management of the pain of each individual patient.

Continual re-evaluation of the patient receiving Morphine Sulfate Injection, USP is important, with special attention to the management of pain and the occurrence of side effects associated with therapy.

2.3 Direct Intravenous Injection

The usual starting dose in adults is 0.1 mg to 0.2 mg per kg every 4 hours as needed to manage pain.

- Inspect Morphine Sulfate Injection for particulate matter and discoloration prior to administration.
- Administer the injection slowly.
- Monitor the patient closely for signs of respiratory and central nervous system depression.

2.4 Intramuscular Injection

The initial IM dose is 10 mg, every 4 hours as needed to manage pain (based on a 70 kg adult).

- Inspect Morphine Sulfate Injection for particulate matter and discoloration prior to administration.
- Monitor the patient closely for signs of respiratory and central nervous system depression.

2.5 Dosing with Hepatic and Renal Impairment

Morphine Sulfate pharmacokinetics have been reported to be significantly altered in patients with cirrhosis and renal failure. Start these patients with lower doses of Morphine Sulfate Injection, USP and titrate slowly while carefully monitoring for respiratory and central nervous system depression *[see Use in Specific Populations (8.7 and 8.8)]*.

3 DOSAGE FORMS AND STRENGTHS

Morphine Sulfate Injection, USP is available in the following strengths for intravenous and intramuscular administration.

- 2 mg/mL in 1 mL prefilled disposable syringe for IV or IM use.
- 4 mg/mL in 1 mL prefilled disposable syringe for IV or IM use.
- 5 mg/mL in 1 mL prefilled disposable syringe for IV or IM use.
- 8 mg/mL in 1 mL prefilled disposable syringe for IV or IM use.
- 10 mg/mL in 1 mL prefilled disposable syringe for IV or IM use.

4 CONTRAINDICATIONS

Morphine sulfate is contraindicated in:

- patients with known hypersensitivity to morphine.
- patients with respiratory depression in the absence of resuscitative equipment.
- patients with acute or severe bronchial asthma or hypercarbia.
- any patient who has or is suspected of having paralytic ileus.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Medication Errors

Morphine Sulfate Injection is available in five concentrations for direct injection. Take care when prescribing and administering Morphine Sulfate Injection to avoid dosing errors due to confusion between different concentrations and between mg and mL, which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed. When writing prescriptions, include both the total dose in mg and the total dose in volume.

5.2 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.

5.3 Respiratory Depression

Respiratory depression is the primary risk of Morphine Sulfate Injection, USP. Respiratory depression occurs more frequently in elderly or debilitated patients and in those suffering from conditions accompanied by hypoxia, hypercapnia or upper airway obstruction, in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation. Morphine administration should be limited to use by those familiar with the management of respiratory depression. Rapid intravenous administration may result in chest wall rigidity.

Patients with chronic obstructive pulmonary disease or cor pulmonale and in patients having a substantially decreased respiratory reserve (e.g., severe kyphoscoliosis), hypoxia, hypercapnia or pre-existing respiratory depression have an increased risk of increased airway resistance and decrease respiratory drive to the point of apnea with use of Morphine Sulfate Injection, USP. Therefore, consider alternative non-opioid analgesics, and use Morphine Sulfate Injection, USP only under careful medical supervision at the lowest effective dose in such patients.

5.4 Central Nervous System (CNS) Toxicity

Excitation of the central nervous system, resulting in convulsion, may accompany high doses of morphine given intravenously. Dysphoric reactions may occur after any size dose and toxic psychoses have been reported.

5.5 Misuse, Abuse and Diversion of Opioids

Morphine sulfate is an opioid agonist and a Schedule II controlled substance. Such drugs are sought by drug abusers and people with addiction disorders. Diversion of Schedule II products is an act subject to criminal penalty *[see Drug Abuse and Dependence (9)]*.

Morphine sulfate can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Morphine Sulfate Injection, USP in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

Concerns about abuse, addiction and diversion should not prevent the proper management of pain. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

5.6 Central Nervous System (CNS) Depressants

The depressant effects of morphine are potentiated by the presence of other CNS depressants such as alcohol, sedatives, antihistamines or psychotropic drugs. Use of morphine in conjunction with other CNS active drugs may increase the risk of respiratory depression, hypotension, profound sedation, coma, or death.

5.7 Increased Intracranial Pressure or Head Injury

Use Morphine Sulfate Injection with extreme caution in patients with head injury or increased intracranial pressure. In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of Morphine Sulfate Injection, USP and its potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated. Pupillary changes (miosis) from morphine may obscure the existence, extent and course of intracranial pathology. Clinicians should maintain a high index of suspicion for adverse drug reactions when evaluating altered mental status or movement abnormalities in patients receiving this modality of treatment.

5.8 Hypotensive Effect

Morphine sulfate may cause severe hypotension in an individual whose ability to maintain their blood pressure has been compromised by a depleted blood volume, shock, impaired myocardial function or concurrent administration of sympatholytic drugs, and drugs such as phenothiazines or general anesthetics. Orthostatic hypotension is a frequent complication in single-dose parenteral morphine analgesia in ambulatory patients.

The vasodilation produced by Morphine Sulfate Injection, USP may further reduce cardiac output and blood pressure in patients in circulatory shock.

5.9 Driving and Operating Machinery

Morphine may impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Caution patients accordingly.

5.10 Gastrointestinal Effects

Do not administer Morphine Sulfate Injection, USP to patients with gastrointestinal obstruction, especially paralytic ileus because Morphine Sulfate Injection, USP diminishes propulsive peristaltic waves in the gastrointestinal tract and may prolong the obstruction. The administration of Morphine Sulfate Injection, USP may obscure the diagnosis or clinical course in patients with acute abdominal condition.

5.11 Use in Biliary Surgery or Disorders of the Biliary Tract

Morphine sulfate should be used with caution in patients with biliary tract disease, including acute pancreatitis, as morphine sulfate may cause spasm of the sphincter of Oddi and diminish biliary and pancreatic secretions.

5.13 Exposure, Hypothermia, Immersion and Shock

Caution must be used when injecting any opioid intramuscularly into chilled areas or in patients with hypotension or shock, since impaired perfusion may prevent complete absorption; if repeated injections are administered, an excessive amount may be suddenly absorbed if normal circulation is re-established.

5.14 Special Risk Groups

Use Morphine Sulfate injection in reduced dosages in patients with severe renal or hepatic impairment, Addison's disease, hypothyroidism, prostatic hypertrophy, or urethral stricture, and in elderly or debilitated patients. Monitor these patients closely for signs of respiratory and central nervous system depression *[see Use in Specific Populations (8)]*.

6 ADVERSE REACTIONS

Serious adverse reactions associated with Morphine Sulfate Injection, USP include respiratory depression, apnea, and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest. Rarely, anaphylactoid reactions have been reported when morphine or other phenanthrene alkaloids of opium are administered intravenously.

The most frequently observed adverse reactions include sedation, lightheadedness, dizziness, nausea, vomiting, constipation and diaphoresis. These effects seem to be more prominent in ambulatory patients and in those who are not experiencing severe pain. Some adverse reactions in ambulatory patients may be alleviated if the patient lies down.

Other possible adverse reactions include:

Central Nervous System – Euphoria, dysphoria, weakness, headache, agitation, tremor, uncoordinated muscle movements, visual disturbances, transient hallucinations and disorientation.

Gastrointestinal – Constipation, biliary tract spasm.

Cardiovascular – Tachycardia, bradycardia, palpitation, faintness, syncope and orthostatic hypotension.

Genitourinary – Oliguria and urinary retention; an antidiuretic effect has been reported.

Allergic – Pruritus, urticaria and skin rashes. Anaphylactoid reactions have been reported following intravenous administration.

Other – Opiate-induced histamine release may be responsible for the flushing of the face, diaphoresis and pruritus often seen with these drugs. Wheals and urticaria at the site of injection are probably related to histamine release. Local tissue irritation, pain and induration have been reported following repeated subcutaneous injection. Morphine may alter temperature regulation in susceptible individuals and will depress the cough reflex.

7 DRUG INTERACTIONS

7.1 Central Nervous System (CNS) Depressants

Central nervous system depressants including other narcotic analgesics, general anesthetics, phenothiazines, tricyclic antidepressants, tranquilizers, sedatives, hypnotics, antiemetics or alcohol increase the risks of respiratory depression, hypotension, profound sedation and coma if given concomitantly with morphine sulfate injection.

7.2 Muscle Relaxants

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

7.3 Mixed Agonist/Antagonist Opioid Analgesics

Do not administer mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine and butorphanol) to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic such as Morphine Sulfate Injection, USP. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic and/or may precipitate withdrawal symptoms.

7.4 Cimetidine

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, USP.

7.5 Monoamine Oxidase Inhibitors (MAOIs)

MAOIs markedly potentiate the action of Morphine Sulfate Injection, USP. Allow at least 14 days after stopping treatment with MAOIs before initiating treatment with Morphine Sulfate Injection, USP.

7.6 Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention, severe constipation or paralytic ileus.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects (Pregnancy Category C)

No formal studies to assess the teratogenic effects of morphine in animals have been conducted. It is also not known whether morphine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Morphine should be given to a pregnant woman only if clearly needed. In humans, the frequency of congenital anomalies have been reported to be no greater than expected among the children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with morphine anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy.

Several literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue and skeletal abnormalities. With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted were characteristic of those observed when maternal toxicity is present. In one study, following subcutaneous infusion of doses greater than or equal to 0.15 mg/kg to mice, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae and malformed xiphoid were noted in the absence of maternal toxicity. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. In rats treated with subcutaneous infusions of morphine during the period of organogenesis, no teratogenicity was observed.

No maternal toxicity was observed in this study however, increased mortality and growth retardation were seen in the offspring. In two studies performed in the rabbit, no evidence of teratogenicity was reported at subcutaneous doses up to 100 mg/kg.

Nonteratogenic Effects

Controlled studies of chronic *in utero* morphine exposure in pregnant women have not been conducted. Infants born to mothers who have taken opioids chronically may exhibit withdrawal symptoms, reversible reduction in brain volume, small size, decreased ventilatory response to CO_2 and increased risk of sudden infant death syndrome. Morphine sulfate should be used by a pregnant woman only if the need for opioid analgesia clearly outweighs the potential risks to the fetus.

Published literature has reported that exposure to morphine during pregnancy is associated with reduction in growth and a host of behavioral abnormalities in the offspring of animals. Morphine treatment during gestational periods of organogenesis in rats, hamsters, guinea pigs and rabbits resulted in the following treatment-related embryotoxicity and neonatal toxicity in one or more studies: decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, delayed motor and sexual maturation, and increased neonatal mortality, cyanosis and hypothermia. Decreased fertility in female offspring 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. Decreased litter size and viability were observed in the offspring of male rats administered morphine (25 mg/kg, ip) for 1 day prior to mating. Behavioral abnormalities resulting from chronic morphine exposure of fetal animals included altered reflex and motor skill development, mild withdrawal and altered responsiveness to morphine persisting into adulthood.

8.2 Labor and Delivery

Morphine readily passes into the fetal circulation and may result in respiratory depression and psycho-physiologic effects in neonates. Naloxone and resuscitative equipment should be available for reversal of narcotic-induced respiratory depression in the neonate. In addition, parenteral morphine may reduce the strength, duration and frequency of uterine contractions resulting in prolonged labor. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Closely observe neonates whose mothers received opioid analgesics during labor for signs of respiratory depression.

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8.3 Nursing Mothers

Low levels of Morphine Sulfate Injection, USP have been detected in maternal milk. The milk:plasma morphine AUC ratio is about 2:5:1. The amount of Morphine Sulfate Injection, USP delivered to the infant depends on the plasma concentration of the mother, the amount of milk ingested by the infant and the extent of first-pass metabolism. Because of the potential for serious adverse reactions in nursing infants from Morphine Sulfate Injection, USP including respiratory depression, sedation and possibly withdrawal symptoms upon cessation of Morphine Sulfate Injection, USP administration to the mother, decide whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of Morphine Sulfate Injection in pediatric patients below the age of 18 have not been established.

8.5 Geriatric Use

The pharmacodynamic effects of morphine in the elderly are more variable than in the younger population. Older patients will vary widely in the effective initial dose, rate of development of tolerance and the frequency and magnitude of associated adverse effects as the dose is increased. Initial doses should be based on careful clinical observation following "test doses" after making due allowances for the effects of the patient's age and infirmity on his/her ability to clear the drug.

Elderly patients may be more susceptible to respiratory depression and/or respiratory arrest following administration of morphine.

In general, use caution when selecting a dose 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.

8.6 Gender

While evidence of greater post-operative Morphine Sulfate Injection, USP consumption in men compared to women is present in the literature, clinically significant differences in analgesic outcomes and pharmacokinetic parameters have not been consistently demonstrated. Some studies have shown an increased sensitivity to the adverse effects of Morphine Sulfate Injection, USP, including respiratory depression, in women compared to men.

8.7 Hepatic Impairment

Morphine sulfate pharmacokinetics have been reported to be significantly altered in patients with cirrhosis. Clearance was found to decrease with a corresponding increase in half-life. The M3G and M6G to morphine AUC ratio is also decreased in these subjects, indicating diminished metabolic activity. Start these patients cautiously with lower doses of Morphine Sulfate Injection, USP and titrate slowly while carefully monitoring for side effects.

8.8 Renal Impairment

Morphine sulfate pharmacokinetics are altered in patients with renal failure. Clearance is decreased and the metabolites, M3G and M6G, may accumulate to much higher plasma levels in patients with renal failure as compared to patients with normal renal function. Start these patients cautiously with lower doses of Morphine Sulfate Injection, USP and titrate slowly while carefully monitoring for side effects.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Morphine sulfate is an opioid agonist and a Schedule II controlled substance. Morphine sulfate, like other opioids, can be abused and is subject to criminal diversion.

9.2 Abuse

Morphine Sulfate Injection, USP contains a potent narcotic which has been associated with abuse and dependence. Abuse is defined as the intentional non-therapeutic use of a drug, even once, for its rewarding psychological or physiological effects. Due to the risk of overdosage and the risk of its diversion and abuse, it is recommended that special measures be taken to control this product within the hospital or clinic.

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

"Drug-seeking" behavior is very common in addicts and drug abusers. 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 physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Drug addiction is characterized by compulsive use, use for non-medical purposes and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-discipline approach, but relapse is common.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence. The converse is also true. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Careful record-keeping of prescribing information, including quantity, frequency and renewal requests is strongly advised.

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

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Use in Specific Populations (8.2)]*.

9.3 Dependence

Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors) and euphoria. Physical dependence and tolerance are frequent during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia and mydriasis. Other 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.

Withdrawal symptoms may occur when morphine is discontinued abruptly or upon administration of a narcotic antagonist. In general, taper morphine rather than abruptly discontinue, especially when used for more than a few days.

10 OVERDOSAGE

10.1 Symptoms

Acute overdosage with morphine is characterized by respiratory depression, with or without concomitant CNS depression. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Morphine sulfate may cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdosage 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 overdose situations.

10.2 Treatment

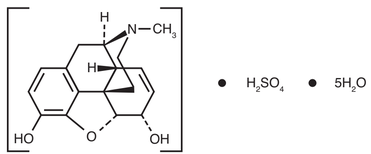
Give primary attention to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Employ supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema accompany overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The opioid antagonist naloxone is a specific antidote to respiratory depression resulting from opioid overdose. Since the duration of reversal is expected to be less than the duration of action of Morphine Sulfate Injection, USP, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to opioid antagonists is sub-optimal or only brief in nature, administer additional antagonist as directed by the manufacturer of the product. Do not administer opioid antagonists in the absence of clinically significant respiratory or circulatory depression secondary to Morphine Sulfate Injection, USP overdose. Administer such agents cautiously to persons who are known or suspected to be physically dependent on Morphine Sulfate Injection, USP. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome.

In an individual physically dependent on opioids, administration of the usual dose 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. Reserve use of an opioid antagonist for cases where such treatment is clearly needed. If it is necessary to treat serious respiratory depression in the physically dependent patient, initiate administration of the antagonist with care and titrate with smaller than usual doses.

11 DESCRIPTION

Morphine sulfate, an opioid agonist, is 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. It is chemically designated as 7,8-Didehydro-4,5-epoxy-17-methyl-(5α,6α)-morphinan-3,6diol sulfate (2: 1) (salt), pentahydrate, with the following structural formula:



● H_2SO_4 ● $5H_2O$

$(C_{17}H_{19}NO_3)_2 \bullet H_2SO_4 \bullet 5H_2O$ Molecular Weight is 758.83

Morphine Sulfate Injection, USP is a sterile, nonpyrogenic solution of Morphine Sulfate Injection, USP, free of antioxidants and preservatives.

Each 1 mL syringe contains 2 mg, 4 mg, 5 mg, 8 mg or 10 mg of Morphine Sulfate, USP in 1 mL total volume with the following inactive ingredients: for the 2 mg/mL and 4 mg/mL, 8.4 mg sodium chloride, 2.3 mg of sodium citrate, 0.74 mg of citric acid, 0.111 mg of edetate disodium, 0.053 mg of calcium chloride and water for injection. For the 5 mg/mL, 8 mg/mL and 10 mg/mL, 7.5 mg sodium chloride, 3.45 mg of sodium citrate, 1.11 mg of citric acid, 0.111 mg of edetate disodium, 0.053 mg of calcium chloride and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Morphine, a full opioid agonist, is relatively selective for the mμ receptor, although it can interact with other opioid receptors at higher doses. In addition to analgesia, the widely diverse effects of morphine sulfate include drowsiness, changes in mood, respiratory depression, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous system.

12.2 Pharmacodynamics

Morphine concentrations are not predictive of analgesic response, especially in patients previously treated with opioids. The minimum effective concentration varies widely and is influenced by a variety of factors, including the extent of previous opioid use, age and general medical condition. Effective doses in tolerant patients may be significantly higher than in opioid-naïve patients.

Onset of analgesia occurs with 5-20 minutes following intramuscular administration of morphine, rising to peak analgesia sixty minutes after a single intramuscular injection. The duration of analgesia after a single injection is usually three to four hours. Morphine and similar opioid analgesics rapidly induce tolerance to their effects, so that the duration of analgesia may be shorter following subsequent doses of morphine. Once patients are started on morphine, the dose required for satisfactory analgesia will rise, with the rate of development of tolerance varying depending on the patient's prior narcotic use, level of pain, degree of anxiety, use of other CNS active drugs, circulatory status, total dose and the inter-dose interval.

Effects on the Central Nervous System (CNS)

The principle therapeutic action of morphine is analgesia. Although the precise mechanism of the analgesic action is unknown, specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression and perception of analgesic effects. In common with other opioids, morphine causes respiratory depression, in part by a direct effect on the brainstem respiratory centers. Morphine and related opioids depress the cough reflex by direct effect on the cough center in the medulla. Morphine causes miosis, even in total darkness.

Effects on the Gastrointestinal Tract and on Other Smooth Muscle

Gastric, biliary and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility and is associated with an increase in tone in the antrum of the stomach 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 is increased to the point of spasm. The end result may be constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi. Morphine may also cause spasm of the sphincter of the urinary bladder.

Effects of the Cardiovascular System

In therapeutic doses, morphine does not usually exert major effects on the cardiovascular system. Morphine produces peripheral vasodilation which may result in orthostatic hypotension and fainting. Release of histamine can occur, which may play a role in opioid-induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol and luteinizing hormones (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and simulated by opioids.

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.

12.3 Pharmacokinetics

Morphine has an apparent volume of distribution ranging from 1.0 to 4.7 L/kg after *intravenous dosage*. Protein binding is low, about 36%, and muscle tissue binding is reported as 54%. A blood-brain barrier exists, and when morphine is introduced outside of the CNS (e.g., *intravenously*), plasma concentrations of morphine remain higher than the corresponding CSF morphine levels.

Average peak morphine plasma levels of 67.4 ± 22.5 ng/mL were noted around 5 to 30 minutes following intramuscular injection of 10 mg morphine sulfate from a prefilled syringe.

Morphine has a total plasma clearance which ranges from 0.9 to 1.2 L/kg/h (liters/kilogram/hour) in postoperative patients, but shows considerable interindividual variation. The major pathway of clearance is hepatic glucuronidation to morphine -3-glucuronide, which is pharmacologically inactive. The major excretion path of the conjugate is through the kidneys, with about 10% in the feces. Morphine is also eliminated by the kidneys, 2 to 12% being excreted unchanged in the urine. Terminal half-life is commonly reported to vary from 1.5 to 4.5 hours, although the longer half-lives were obtained when morphine levels were monitored over protracted periods with very sensitive radioimmunoassay methods. The accepted elimination half-life in normal subjects is 1.5 to 2 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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 also 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 these 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, higher incidence of pseudopregnancies and reduction in implantation sites were seen. Studies from the literature have also reported changes in hormonal levels (i.e. testosterone, luteinizing hormone, serum corticosterone) following treatment with morphine. These changes may be associated with the reported effects on fertility in the rat.

16 HOW SUPPLIED/STORAGE AND HANDLING

Morphine Sulfate Injection, USP is available for intravenous (IV) or intramuscular (IM) use as:

2 mg/mL in 1 mL pre-filled disposable syringe, NDC 76045-004-10
4 mg/mL in 1 mL pre-filled disposable syringe, NDC 76045-005-10
5 mg/mL in 1 mL pre-filled disposable syringe, NDC 76045-006-10
8 mg/mL in 1 mL pre-filled disposable syringe, NDC 76045-007-10
10 mg/mL in 1 mL pre-filled disposable syringe, NDC 76045-008-10

Available in a carton of twenty-four (24) syringes for each strength.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

PROTECT FROM LIGHT. DO NOT FREEZE.

This product is for single dose only.

Contains no preservative or antioxidant.

DISCARD ANY UNUSED PORTION.

DO NOT HEAT-STERILIZE. DO NOT place syringe on a sterile field.

DO NOT autoclave syringe.

DO NOT introduce any other fluid into the syringe at any time.

Retain in carton until time of use.

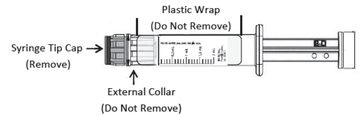
All steps must be done sequentially.

INSTRUCTIONS FOR USE

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if color is darker than pale yellow, if it is discolored in any other way or if it contains a precipitate.

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



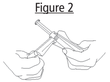
1. Inspect the outer packaging (blister pack) by verifying:
   - blister integrity
   - drug name
   - drug strength
   - dose volume
   - route of administration
   - expiration date to be sure that the drug has not expired
   - sterile field applicability

   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. Once the syringe is removed, if applicable, discard the StabilOx® CANISTER contained at the end of the blister pack. (See Figure 2)

Figure 2

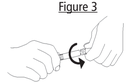


4. Perform visual inspection on the syringe by verifying:
   - absence of syringe damage
   - absence of external particles
   - absence of internal particles
   - proper drug color
   - expiration date to be sure that the drug has not expired
   - drug name
   - drug strength
   - dose volume
   - route of administration
   - 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 the medication with a needle, to prevent needle stick injuries, do not recap needle.

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 dose only

For more information concerning this drug, please call Fresenius Kabi USA, LLC at 1-800-551-7176.

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

17 PATIENT COUNSELING INFORMATION

Physicians should provide the following information to patients receiving parenteral morphine:

- Morphine analgesics may produce orthostatic hypotension in ambulatory patients.
- There is potential for severe constipation; appropriate laxatives and/or stool softeners as well as other appropriate treatments should be initiated from the onset of opioid therapy.
- Analgesic doses of morphine cloud judgment and impair the mental and/or physical abilities required for the performance of tasks such as driving a vehicle or operating machinery.
- Morphine will add to the effect of alcohol and other CNS depressants, including sedatives, hypnotics, tranquilizers, phenothiazines and antihistamines.
- The most common adverse events that may occur while taking morphine include nausea, somnolence, lightheadedness, dizziness, sedation, vomiting, diaphoresis and constipation.

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FRESENIUS KABI
Lake Zurich, IL 60047

www.fresenius-kabi.us

D1030P01
Rev. 5/2016