

Simplist® MicroVault® packaging supports diversion deterrence

Simplist® MicroVault® Packaging

- ✔ Makes narcotic inventory management easier with 5-pack bundling and 10-pack cartons
- ✔ Supports secure dispensing with hard plastic packaging and tamper evident seal
- ✔ Saves space with slim packaging



Dilaudid® (HYDROMORPHONE HCl) Injection, USP.

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- DILAUID INJECTION exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions.
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase.
- Prolonged use of DILAUID INJECTION during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
- 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 for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.

Please see full Important Safety Information, including Boxed Warning, for Dilaudid® (HYDROMORPHONE HCl) Injection, USP on the following pages.

Simplist® Morphine Sulfate Injection, USP.

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

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- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase.
- Prolonged use of Morphine Sulfate Injection during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
- 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 for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.

Please see full Important Safety Information, including Boxed Warning, for Morphine Sulfate Injection, USP on the following pages.

Simplist®
Ready-to-administer prefilled syringes

**FRESENIUS
KABI**
caring for life

To place an order, contact your Sales Representative or call Customer Service at 1.888.386.1300
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www.simplist-us.com | 1.888.386.1300

Simplist® Dilaudid® MicroVault®

Ready-to-administer prefilled syringe packaging



MicroVault® dimensions:
3.625" x .75"

MicroVault® carton dimensions:
3.125" x 2.625" x 4.375"
10-pack carton
Packaged in bundles of 5



Unit of Sale NDC Number (PK)	76045-121-11	76045-009-06	76045-009-11
Description	Single Dose Simplist® Syringe	Single Dose Simplist® Syringe	Single Dose Simplist® Syringe
Strength	0.2 mg per 1 mL	0.5 mg per 0.5 mL	1 mg per 1 mL
Concentration	0.2 mg per 1 mL	0.5 mg per 0.5 mL	1 mg per 1 mL
Fill Volume	1 mL	0.5 mL	1 mL
Unit of Sale	10	10	10
Bar Code			

INDICATIONS AND USE

DILAUID INJECTION is indicated for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate.

Limitations of Use: Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve DILAUID INJECTION for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]; have not been tolerated, are not expected to be tolerated, have not provided adequate analgesia, or are not expected to provide adequate analgesia

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

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- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase.
- Prolonged use of DILAUID INJECTION during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
- 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 for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.

DILAUID INJECTION is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment, known or suspected gastrointestinal obstruction, including paralytic ileus, known hypersensitivity to hydromorphone, hydromorphone salts, sulfite-containing medications, or any other components of the product.

Life-threatening respiratory depression in patients with chronic pulmonary disease or in elderly, cachectic, or debilitated patients: Monitor closely, particularly during initiation and titration.

Adrenal insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid.

Severe hypotension: Monitor during dosage initiation and titration. Avoid use in patients with circulatory shock.

Risks of use in patients with increased intracranial pressure, brain tumors, head injury, or impaired consciousness: Monitor for sedation and respiratory depression. Avoid use patients with impaired consciousness or coma.

DILAUID INJECTION contains sodium metabisulfite. There is a risk of anaphylactic symptoms and life-threatening asthmatic episodes in susceptible people.

Additional serious adverse reactions: Apnea, circulatory depression, respiratory arrest, shock, cardiac arrest, seizures, withdrawal, anaphylaxis. Most common adverse reactions: Lightheadedness, dizziness, sedation, nausea, vomiting, sweating, flushing, dysphoria, euphoria, dry mouth, and pruritus.

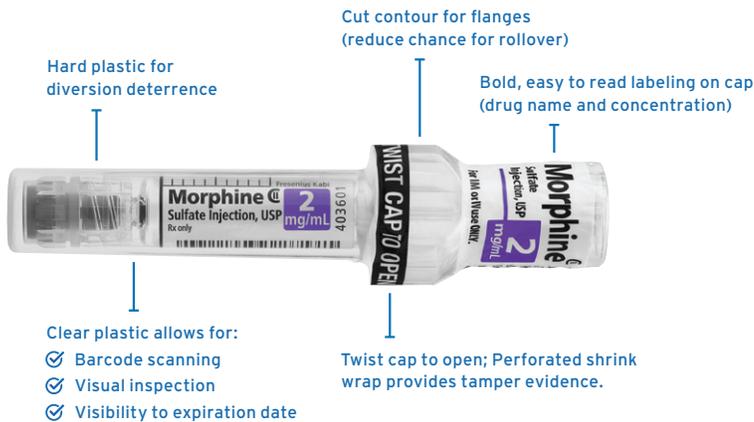
To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176, option 5, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Overdosage: Acute overdose can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, miosis (or mydriasis when hypoxia is present), and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death.

This Important Safety Information does not include all the information needed to use DILAUID safely and effectively. Please see full prescribing information, including BOXED WARNING, for DILAUID INJECTION available at www.fresenius-kabi.com/us.

Simplist® Morphine MicroVault®

Ready-to-administer prefilled syringe packaging



MicroVault® dimensions:
3.625" x .75"

MicroVault® carton dimensions:
3.125" x 2.625" x 4.375"
10-pack carton
Packaged in bundles of 5



Unit of Sale NDC Number (PK)	76045-004-11	76045-005-11
Description	Single Dose Simplist® Syringe	Single Dose Simplist® Syringe
Strength	2 mg per 1 mL	4 mg per 1 mL
Concentration	2 mg per 1 mL	4 mg per 1 mL
Fill Volume	1 mL	1 mL
Unit of Sale	10	10
Bar Code		

INDICATIONS AND USE

Morphine Sulfate Injection is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use: Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve Morphine Sulfate Injection for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or opioid combination products); have not been tolerated, are not expected to be tolerated, have not provided adequate analgesia, or are not expected to provide adequate analgesia.

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- Morphine Sulfate Injection exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions.
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase.
- Prolonged use of Morphine Sulfate Injection during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
- 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 for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.

Morphine Sulfate Injection is contraindicated in patients with: significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days, known or suspected gastrointestinal obstruction, including paralytic ileus, and hypersensitivity to morphine.

Cardiovascular Instability: High doses are excitatory. Have Naloxone Injection and resuscitative equipment immediately available.

Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration.

Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid.

Severe Hypotension: Monitor during dosage initiation and titration. Avoid 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: Monitor for sedation and respiratory depression. Avoid use of Morphine Sulfate Injection in patients with impaired consciousness or coma.

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

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC, at 1-800-551-7176 option 5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Overdosage: Acute overdose with Morphine Sulfate Injection 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, partial or complete airway obstruction, snoring, and death.

This important safety information does not include all the information needed to use MORPHINE SULFATE INJECTION safely and effectively. Please see full prescribing information, including BOXED WARNING, for MORPHINE SULFATE INJECTION available at www.fresenius-kabi.com/us.

DILAUDID® INJECTION (hydromorphone hydrochloride) for intravenous, intramuscular, or subcutaneous use, CII

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This brief summary does not include all the information needed to use DILAUDID INJECTION safely and effectively. Please see full prescribing information, including BOXED WARNING, for DILAUDID INJECTION at www.fresenius-kabi.com/us.

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISK FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

DILAUDID 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 DILAUDID INJECTION and monitor all patients regularly for the development of these behaviors and conditions [see Warnings and Precautions].

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of DILAUDID INJECTION. Monitor for respiratory depression, especially during initiation of DILAUDID INJECTION or following a dose increase [see Warnings and Precautions].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of DILAUDID INJECTION during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Warnings and Precautions].

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings and Precautions and Drug Interactions].

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

INDICATIONS AND USAGE

DILAUDID INJECTION is an opioid agonist indicated for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses [see Warnings and Precautions], reserve DILAUDID INJECTION for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

CONTRAINDICATIONS [see Warnings and Precautions]

DILAUDID INJECTION is contraindicated in patients with:

- Significant respiratory depression.
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment.
- Known or suspected gastrointestinal obstruction, including paralytic ileus.
- Known hypersensitivity to hydromorphone, hydromorphone salts, any other components of the product, or sulfite-containing medications (e.g. anaphylaxis).

WARNINGS AND PRECAUTIONS [also see BOXED WARNING]

• **Addiction, Abuse, and Misuse:** As an opioid, DILAUDID INJECTION exposes patients and other users to the risks of opioid addiction, abuse, and misuse [see Drug Abuse and Dependence]. Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing DILAUDID INJECTION and monitor all patients receiving DILAUDID INJECTION for the development of these behaviors and conditions.

• **Life-Threatening Respiratory Depression:** Serious, life-threatening, or fatal respiratory depression may occur with use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases of DILAUDID INJECTION. 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.

• **Neonatal Opioid Withdrawal Syndrome:** Prolonged use of DILAUDID INJECTION during pregnancy can result in withdrawal in the neonate. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Use in Specific Populations, Patient Counseling Information].

• **Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants:** Profound sedation, respiratory depression, coma, and death may result from the concomitant use of DILAUDID Injection with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). 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. Follow patients closely for signs and symptoms of respiratory depression and sedation.

• **Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients:** Monitor closely at initiation, dose titration, and when DILAUDID INJECTION is given concomitantly with other drugs that depress respiration. [See Contraindications for use in patients with bronchial asthma]

• **Adrenal Insufficiency:** If diagnosed, wean the patient off of the opioid and treat with physiologic replacement doses of corticosteroids.

• **Severe Hypotension:** Monitor during dosage initiation and titration. Avoid use in patients with circulatory shock.

• **Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness:** Monitor for sedation and respiratory depression. Avoid use of DILAUDID INJECTION in patients with impaired consciousness or coma.

• **Risks of Use in Patients with Gastrointestinal Conditions:** DILAUDID INJECTION is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The hydromorphone in DILAUDID 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.

• **Increased Risk of Seizures in Patients with Seizure Disorders:** Monitor patients with a history of seizure disorders for worsened seizure control.

• **Withdrawal:** When discontinuing DILAUDID INJECTION in a physically-dependent patient, gradually taper the dosage. Do not abruptly discontinue therapy in physically-dependent patients.

• **Risks of Driving and Operating Machinery:** DILAUDID 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 DILAUDID INJECTION and know how they will react to the medication.

• **Sulfites:** DILAUDID INJECTION contains sodium metabisulfite. [see Contraindications]

• **Increased Risk of Hypotension and Respiratory Depression with Rapid Intravenous Administration:** intravenous injection should be given very slowly.

ADVERSE REACTIONS [see Boxed Warning and Warnings and Precautions]

Serious adverse reactions: Addiction, abuse, and misuse, life-threatening respiratory depression, neonatal opioid withdrawal syndrome, interactions with benzodiazepines and other CNS depressants, adrenal insufficiency, severe hypotension, gastrointestinal adverse reactions, seizures, withdrawal, respiratory depression and apnea, circulatory depression, respiratory arrest, shock, and cardiac arrest.

Most common adverse reactions: Lightheadedness, dizziness, sedation, nausea, vomiting, sweating, flushing, dysphoria, euphoria, dry mouth, and pruritus.

Less frequently observed adverse reactions: tachycardia, bradycardia, palpitations, blurred vision, diplopia, miosis, visual impairment, constipation, ileus, diarrhea, abdominal pain, weakness, feeling abnormal, chills, injection site urticaria, fatigue, injection site reactions, peripheral edema, biliary colic, anaphylactic reactions, hypersensitivity reactions, increase in hepatic enzymes, decreased appetite, muscle rigidity, headache, tremor, paraesthesia, nystagmus, increased intracranial pressure, syncope, taste alteration, involuntary muscle contractions, presyncope, convulsion, drowsiness, dyskinesia, hyperalgesia, lethargy, myoclonus, somnolence, agitation, mood altered, nervousness, anxiety, depression, hallucination, disorientation, insomnia, abnormal dreams, urinary retention, urinary hesitation, antidiuretic effects, erectile dysfunction, bronchospasm, laryngospasm, dyspnea, oropharyngeal swelling, injection site pain, urticaria, rash, hyperhidrosis, flushing, hypotension, hypertension, serotonin syndrome, adrenal insufficiency, anaphylaxis, and androgen deficiency.

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

DRUG INTERACTIONS

Clinically significant drug interactions with DILAUDID INJECTION: benzodiazepines and other CNS depressants, serotonergic drugs, monoamine oxidase inhibitors (MAOIs), mixed agonist/antagonist and partial agonist opioid analgesics, muscle relaxants, diuretics and anticholinergic drugs.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** May cause fetal harm [see BOXED WARNING for neonatal opioid withdrawal syndrome].
- **Labor or Delivery:** Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. Naloxone must be available for reversal. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.
- **Lactation:** Low levels of opioid analgesics have been detected in human milk. Monitor infants for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of hydromorphone is stopped, or when breast-feeding is stopped.
- **Females and Males of Reproductive Potential:** Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.
- **Pediatric Use:** The safety and effectiveness of DILAUDID INJECTION in pediatric patients has not been established.
- **Geriatric Use:** Patients 65 years of age or older may have increased sensitivity to hydromorphone. Start at the low end of the dosing range, titrate the dosage slowly and monitor for signs of CNS and respiratory depression.
- **Hepatic and Renal Impairment:** The pharmacokinetics of hydromorphone are affected by hepatic and renal impairment. Start patients on one-fourth to one-half the usual starting dose depending on the degree of impairment and closely monitor during dose titration.

OVERDOSAGE

Acute overdose with DILAUDID INJECTION 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, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis, rather than miosis, may be seen with hypoxia in overdose situations. In case of overdose, reestablish patent and protected airway, institute assisted or controlled ventilation, manage circulatory shock, pulmonary edema, cardiac arrest or arrhythmias, as indicated. Administer opioid antagonists only for clinically significant respiratory or circulatory depression secondary to hydromorphone overdose. Carefully monitor the patient until spontaneous respiration is reestablished. Administration of opioid antagonist in a physically dependent patient should be initiated with care and by titration with smaller than usual doses of the antagonist.

Morphine Sulfate Injection, USP CII for intravenous or intramuscular use.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This brief summary does not include all the information needed to use MORPHINE SULFATE INJECTION, USP safely and effectively. Please see full prescribing information, including BOXED WARNING, for MORPHINE SULFATE INJECTION, USP at www.fresenius-kabi.com/us.

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; NEONATAL OPIOID WITHDRAWAL SYNDROME; AND RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

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 Morphine Sulfate Injection, and monitor all patients regularly for the development of these behaviors and conditions [see *Warnings and Precautions*].

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Morphine Sulfate Injection. Monitor for respiratory depression, especially during initiation of Morphine Sulfate Injection, or following a dose increase. Because of delay in maximum CNS effect with intravenously administered morphine (30 min), rapid IV administration may result in overdosing [see *Warnings and Precautions*].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of Morphine Sulfate Injection during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Warnings and Precautions*].

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions and Drug Interactions*].

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

INDICATIONS AND USAGE

Morphine Sulfate Injection is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses [see *Warnings and Precautions*], reserve Morphine Sulfate Injection for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or opioid combination products):

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

CONTRAINDICATIONS

Morphine Sulfate Injection is contraindicated in patients with:

- Significant respiratory depression [see *Warnings and Precautions*].
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see *Warnings and Precautions*].
- Concomitant use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days [see *Warnings and Precautions*].
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see *Warnings and Precautions*].
- Hypersensitivity to morphine (e.g. anaphylaxis) [see *Adverse Reactions*].

WARNINGS AND PRECAUTIONS [also see BOXED WARNING]

- **Addiction, Abuse, and Misuse:** Morphine Sulfate Injection exposes patients and other users to the risks of opioid addiction, abuse,

and misuse, which can lead to overdose and death [see *Drug Abuse and Dependence*]. Assess each patient's risk prior to prescribing Morphine Sulfate Injection, and monitor all patients regularly for the development of these behaviors and conditions.

- **Life-Threatening Respiratory Depression:** Serious, life-threatening, or fatal respiratory depression may occur with use of Morphine Sulfate Injection. Monitor for respiratory depression, especially during initiation of Morphine Sulfate Injection, or following a dose increase. Because of delay in maximum CNS effect with intravenously administered morphine (30 min), rapid IV administration may result in overdosing [see *Overdosage*]. 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.
 - **Neonatal Opioid Withdrawal Syndrome:** Prolonged use of Morphine Sulfate Injection during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Use in Specific Populations*].
 - **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 or other CNS depressants (e.g. non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). 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. Follow patients closely for signs and symptoms of respiratory depression and sedation.
 - **Cardiovascular Instability:** High doses are excitatory. Have Naloxone Injection and resuscitative equipment immediately available.
 - **Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients:** Monitor closely, particularly during dose initiation and titration.
 - **Interactions with Monoamine Oxidase Inhibitors (MAOIs):** Morphine Sulfate Injection should not be used in patients taking MAOIs or within 14 days of stopping such treatment.
 - **Adrenal Insufficiency:** If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid.
 - **Severe Hypotension:** Monitor during dosage initiation and titration. Avoid 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:** Monitor for sedation and respiratory depression. Avoid 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.
 - **Increased Risk of Seizures in Patients with Seizure Disorders:** Monitor patients with a history of seizure disorders for worsened seizure control.
 - **Withdrawal:** Use of mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms.
 - **Central Nervous System Toxicity:** Dysphoric reactions may occur after any size dose and toxic psychoses have been reported.
 - **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.
 - **Risks 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.
- ADVERSE REACTIONS [see Boxed Warning and Warnings and Precautions]**
- Serious adverse reactions associated with Morphine Sulfate Injection included:** addiction, abuse, and misuse, life-threatening respiratory depression, neonatal opioid withdrawal syndrome,

interactions with benzodiazepines or other CNS depressants, cardiac instability, adrenal insufficiency, severe hypotension, gastrointestinal adverse reactions, seizures, withdrawal, 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 included: sedation, lightheadedness, dizziness, nausea, vomiting, constipation and diaphoresis.

Other possible adverse reactions include: euphoria, dysphoria, weakness, headache, agitation, tremor, uncoordinated muscle movements, visual disturbances, transient hallucinations and disorientation, constipation, biliary tract spasm, tachycardia, bradycardia, palpitation, faintness, syncope, orthostatic hypotension, oliguria and urinary retention, pruritus, urticaria, skin rashes, opioid-induced histamine release (flushing of the face, diaphoresis, pruritus, and wheals and urticaria at the site of injection), androgen deficiency, anaphylaxis, serotonin syndrome, and adrenal insufficiency.

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

Clinically significant drug interactions with Morphine Sulfate Injection: benzodiazepines and other central nervous system (CNS) depressants; serotonergic drugs; monoamine oxidase inhibitors (MAOIs); mixed agonist/antagonist and partial agonist opioid analgesics; muscle relaxants; cimetidine; diuretics; anticholinergic drugs; and oral P2Y12 inhibitors.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** May cause fetal harm [see BOXED WARNING for Neonatal Opioid Withdrawal Syndrome].
- **Labor or Delivery:** Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. Naloxone must be available for reversal for opioid-induced respiratory depression. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.
- **Lactation:** Present in breast milk. Lactation studies have not been conducted and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Monitor infants for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of opioid analgesic is stopped, or when breast-feeding is stopped.
- **Females and Males of Reproductive Potential:** Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.
- **Pediatric Use:** The safety and effectiveness in pediatric patients below the age of 18 have not been established.
- **Geriatric Use:** Elderly patients (aged 65 years or older) may have increased sensitivity to morphine. Monitor for signs of central nervous system and respiratory depression. Start at the low end of the dosing range, titrate the dosage slowly and monitor for signs of CNS and respiratory depression.
- **Hepatic and Renal Impairment:** Morphine sulfate pharmacokinetics are altered in patients with cirrhosis and renal failure. Start these patients with a lower than normal dosage and monitor for signs of respiratory depression, sedation, and hypotension.

OVERDOSAGE

Acute overdose with Morphine Sulfate Injection 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, partial or complete airway obstruction, snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in 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 techniques. The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. 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.