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

Simplist® Fentanyl Citrate Injection, USP.

WARNING: RISK OF ADDICTION, ABUSE, AND MISUSE; LIFE- THREATENING RESPIRATORY DEPRESSION; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- **Fentanyl Citrate 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.**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of fentanyl.**
- **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 Fentanyl Citrate Injection, USP on the following pages.

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.

- **DILAUDID 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 DILAUDID 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.

- **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.**

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

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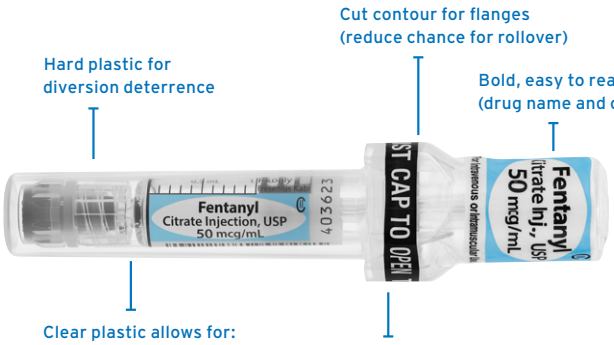
Simplist® Fentanyl MicroVault®

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)	63323-808-11
Description	Single Dose Simplist® Syringe
Strength	50 mcg per 1 mL
Concentration	50 mcg per 1 mL
Fill Volume	1 mL
Unit of Sale	10
Bar Code	N(01)30363323808113

INDICATIONS AND USAGE

Fentanyl Citrate Injection, for intravenous or intramuscular use, is indicated for:

- Analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance and in the immediate postoperative period (recovery room) as the need arises.
- Use as an opioid analgesic supplement in general or regional anesthesia.
- Administration with a neuroleptic as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.
- Use as an anesthetic agent with oxygen in selected high risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopedic procedures.

Fentanyl Citrate Injection should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids. Ensure that an opioid antagonist, resuscitative and intubation equipment, and oxygen are readily available.

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF ADDICTION, ABUSE, AND MISUSE; LIFE- THREATENING RESPIRATORY DEPRESSION; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- **Fentanyl Citrate 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.**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of fentanyl.**
- **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.**

Fentanyl Citrate Injection is contraindicated in patients with a hypersensitivity to fentanyl.

Risks of Skeletal Muscle Rigidity and Skeletal Muscle Movement: Manage with neuromuscular blocking agent. See full prescribing information for more detail on managing these risks.

Severe Cardiovascular Depression: Monitor during dosage initiation and titration.

Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue Fentanyl Citrate Injection if serotonin syndrome is suspected.

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

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, or Head Injury: Monitor for sedation and respiratory depression.

The most common serious adverse reactions were respiratory depression, apnea, rigidity, and bradycardia.

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.

Concomitant Use of CNS Depressants: May decrease pulmonary arterial pressure and may cause hypotension. See full prescribing information for management instructions. For post-operative pain, start with the lowest effective dosage and monitor for potentiation of CNS depressant effects.

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with Fentanyl Citrate Injection because they may reduce the analgesic effect of Fentanyl Citrate Injection or precipitate withdrawal symptoms.

Pregnancy: May cause fetal harm.

Lactation: Infants exposed to Fentanyl Citrate Injection through breast milk should be monitored for excess sedation and respiratory depression.

Geriatric Patients: Titrate slowly and monitor for CNS and respiratory depression.

This Important Safety Information does not include all the information needed to use Fentanyl Citrate Injection, safely and effectively. Please see full prescribing information, including Boxed Warning, for Fentanyl Citrate Injection at www.fresenius-kabi.com/us.

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Simplist® Dilaudid® MicroVault®

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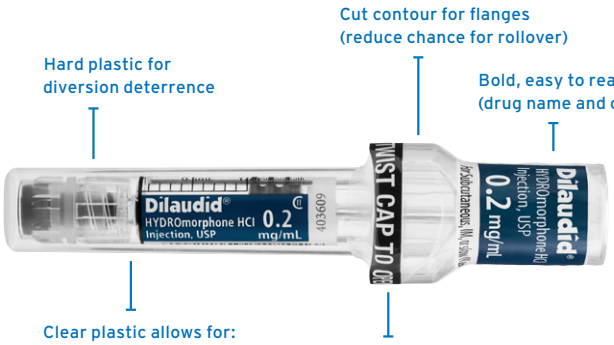

MicroVault® dimensions:
3.625" x .75"

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	N(01)30376045121118	N(01)30376045009065	N(01)30376045009119

INDICATIONS AND USAGE

DILAUDID 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 DILAUDID 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.

- **DILAUDID 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 DILAUDID 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.**

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, 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 of DILAUDID 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 DILAUDID INJECTION in patients with impaired consciousness or coma.

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

Most common adverse reactions are 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 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Serotenergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue DILAUDID INJECTION if serotonin syndrome is suspected.

Monoamine Oxidase Inhibitors (MAOIs): Can potentiate the effects of hydromorphone. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI.

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with DILAUDID INJECTION because they may reduce analgesic effect of DILAUDID INJECTION or precipitate withdrawal symptoms.

Pregnancy: May cause fetal harm.

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.

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

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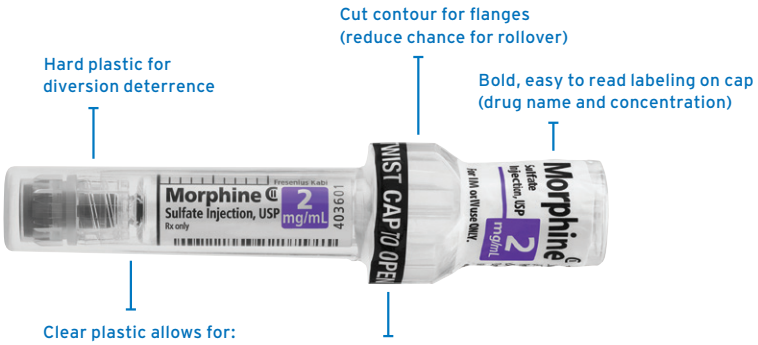

MicroVault® dimensions:
3.625" x .75"

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	N(01)30376045004114	N(01)30376045005111

INDICATIONS AND USAGE

Morphine Sulfate Injection is an opioid agonist 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, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

IMPORTANT SAFETY INFORMATION

WARNING: 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.
- 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 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue Morphine Sulfate Injection if serotonin syndrome is suspected.

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with Morphine Sulfate Injection because they may reduce analgesic effect of Morphine Sulfate Injection or precipitate withdrawal symptoms.

Pregnancy: May cause fetal harm.

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.

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 at www.fresenius-kabi.com/us.

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Simplist® Fentanyl Citrate 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 Fentanyl Citrate Injection safely and effectively. Please see full prescribing information including BOXED WARNING, for Fentanyl Citrate Injection, at www.fresenius-kabi.com/us.

Fentanyl Citrate Injection, for intravenous or intramuscular use, CII

WARNING: RISK OF ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENINGRESPIRATORY DEPRESSION; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

Fentanyl Citrate 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 Fentanyl Citrate 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 Fentanyl Citrate Injection. Monitor for respiratory depression, especially during initiation of Fentanyl Citrate Injection or following a dose increase *[see Warnings and Precautions]*.

Cytochrome P450 3A4 Interaction

The concomitant use of Fentanyl Citrate Injection with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving Fentanyl Citrate Injection and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions, Drug Interactions, Clinical Pharmacology]*

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, Drug Interactions]*.

- **Reserve concomitant prescribing of Fentanyl Citrate 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

Fentanyl Citrate Injection is indicated for:

- analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance, and in the immediate postoperative period (recovery room) as the need arises.
- use as a narcotic analgesic supplement in general or regional anesthesia.
- administration with a neuroleptic as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.
- use as an anesthetic agent with oxygen in selected high risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopedic procedures.

Important Dosage and Administration Instructions

Fentanyl Citrate Injection should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

- Ensure that an opioid antagonist, resuscitative and intubation equipment, and oxygen are readily available.
- Individualize dosage based on factors such as age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.
- Monitor vital signs routinely.

CONTRAINDICATIONS

Fentanyl Citrate Injection is contraindicated in patients with:

- Hypersensitivity to fentanyl (e.g., anaphylaxis) *[See Adverse Reactions]*

WARNINGS AND PRECAUTIONS *[Also see Boxed Warning]*

Addiction, Abuse, and Misuse

Fentanyl Citrate Injection contains fentanyl, a Schedule II controlled substance. As an opioid, Fentanyl Citrate Injection exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence]*.

Opioids are sought by drug users and people with addiction disorders and are subject to criminal diversion. Consider these risks when handling Fentanyl Citrate Injection. Strategies to reduce these risks include proper product storage and control practices for a C-II drug. 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-threatening, 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. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anesthetic doses of Fentanyl Citrate Injection. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression. 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 (CO2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

To reduce the risk of respiratory depression, proper dosing and titration of Fentanyl Citrate Injection are essential. As with other potent opioids, the respiratory depressant effect of Fentanyl Citrate Injection may persist longer than the measured analgesic effect. The total dose of all opioid agonists administered should be considered by the practitioner before ordering opioid analgesics during recovery from anesthesia.

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics can alter respiration by blocking intercostal nerves. Through other mechanisms [see Clinical Pharmacology)] Fentanyl Citrate Injection can also alter respiration. Therefore, when Fentanyl Citrate Injection is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

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 Fentanyl Citrate Injection. Elderly, cachectic, or debilitated patients may have altered pharmacokinetics or altered clearance compared to younger, healthier patients resulting in greater risk for respiratory depression.

Monitor patients closely including vital signs, particularly when initiating and titrating Fentanyl Citrate Injection and when Fentanyl Citrate Injection is given concomitantly with other drugs that depress respiration. To reduce the risk of respiratory depression, proper dosing and titration of Fentanyl Citrate Injection are essential [see Dosage and Administration].

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 of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of Fentanyl Citrate Injection with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of fentanyl and prolong opioid adverse reactions, which may exacerbate respiratory depression *[see Warnings and Precautions]*, particularly when an inhibitor is added after a stable dose of Fentanyl Citrate Injection is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Fentanyl Citrate Injection-treated patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions. When using Fentanyl Citrate Injection with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Fentanyl Citrate Injection-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Fentanyl Citrate Injection *[see Dosage and Administration, Drug Interactions]*.

Concomitant use of Fentanyl Citrate Injection with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor, could result in lower than expected fentanyl plasma concentrations and, decrease efficacy. When using Fentanyl Citrate Injection with CYP3A4 inducers, or discontinuation of a CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the fentanyl Citrate Injection dosage *[see Dosage and Administration, Drug Interactions]*.

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

When benzodiazepines or other CNS depressants are used with Fentanyl Citrate Injection, pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high dose or anesthetic dosages of Fentanyl Citrate Injection are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

When Fentanyl Citrate Injection is used with CNS depressants, hypotension can occur. If it occurs, consider the possibility of hypovolemia and manage with appropriate parenteral fluid therapy. When operative conditions permit, consider repositioning the patient to improve venous return to the heart. Exercise care in moving and repositioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, consider administration of pressor agents other than epinephrine. Epinephrine may paradoxically decrease blood pressure in patients treated with a neuroleptic that blocks alpha adrenergic activity.

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Fentanyl Citrate Injection with benzodiazepines or other CNS depressants (e.g., nonbenzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). If the decision is made to manage postoperative pain with Fentanyl Citrate Injection concomitantly with a benzodiazepine or other CNS depressant, start dosing with the lowest effective dosage and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression, sedation, and hypotension. Fluids or other measures to counter hypotension should be available *[see Drug Interactions]*.

Risks of Muscle Rigidity and Skeletal Muscle Movement

Fentanyl Citrate Injection may cause muscle rigidity, particularly involving the muscles of respiration. The incidence and severity of muscle rigidity is dose related. These effects are related to the dose and speed of injection. Skeletal muscle rigidity also has been reported to occur or recur infrequently in the extended postoperative period usually following high dose administration. In addition, skeletal muscle movements of various groups in the extremities, neck, and external eye have been reported during induction of anesthesia with Fentanyl Citrate Injection; these reported movements have, on rare occasions, been strong enough to pose patient management problems.

These effects are related to the dose and speed of injection and its incidence can be reduced by: 1) administration of up to 1/4 of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of Fentanyl Citrate Injection; 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of eyelash reflex when Fentanyl Citrate Injection is used in anesthetic doses titrated by slow intravenous infusion; or, 3) simultaneous administration of Fentanyl Citrate Injection and a full paralyzing dose of a neuromuscular blocking agent when Fentanyl Citrate Injection is used in rapidly administered anesthetic dosages. The neuromuscular blocking agent used should be compatible with the patient's cardiovascular status.

Severe Cardiovascular Depression

Fentanyl Citrate Injection may cause severe bradycardia, severe hypotension including orthostatic hypotension, and syncope. 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]*. In patients with circulatory shock, Fentanyl Citrate Injection may cause vasodilation that can further reduce cardiac output and blood pressure. Monitor these patients for signs of hypotension after initiating or titrating the dosage of Fentanyl Citrate Injection.

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Serotonin Syndrome with Concomitant Use of Serotonergic Drugs
Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of fentanyl with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazadone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) *[see Drug Interactions]*. This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue Fentanyl Citrate Injection if serotonin syndrome is suspected.

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

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, or Head Injury
In patients who may be susceptible to the intracranial effects of CO2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), Fentanyl Citrate Injection may reduce respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Monitor such patients for signs of increasing intracranial pressure.

Risks of Use in Patients with Gastrointestinal Conditions
Fentanyl 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 Risks of Seizures in Patients with Seizure Disorders
Fentanyl may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical setting associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Fentanyl Citrate Injection therapy.

Risks of Driving and Operating Machinery
Fentanyl Citrate Injection may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery after Fentanyl Citrate Injection administration.

Risks due to Interaction with Neuroleptic Agents
Many neuroleptic agents have been associated with QT prolongation, torsades de pointes, and cardiac arrest. Administer neuroleptic agents with extreme caution in the presence of risk factors for development of prolonged QT syndrome and torsades de pointes, such as: 1) clinically significant bradycardia (less than 50 bpm), 2) any clinically significant cardiac disease, including baseline prolonged QT interval, 3) treatment with Class I and Class III antiarrhythmics, 4) treatment with monoamine oxidase inhibitors (MAOI's), 5) concomitant treatment with other drug products known to prolong the QT interval and 6) electrolyte imbalance, in particular hypokalemia and hypomagnesemia, or concomitant treatment with drugs (e.g. diuretics) that may cause electrolyte imbalance.

Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of Fentanyl Citrate Injection combined with a neuroleptic. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

ECG monitoring is indicated when a neuroleptic agent is used in conjunction with Fentanyl Citrate Injection as an anesthetic premedication, for the induction of anesthesia, or as an adjunct in the maintenance of general or regional anesthesia.

When fentanyl Citrate Injection is used with a neuroleptic and an EEG is used for postoperative monitoring, the EEG pattern may return to normal slowly.

ADVERSE REACTIONS
The following serious adverse reactions are described, or described in greater detail, in other sections:
- Addiction, Abuse, and Misuse *[see Warnings and Precautions]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions]*
- Interactions with Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions]*
- Serotonin Syndrome *[see Warnings and Precautions]*
- Severe Cardiovascular Depression *[see Warnings and Precautions]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions]*
- Seizures *[see Warnings and Precautions]*

The following adverse reactions associated with the use of fentanyl 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.

As with other opioid agonists, the most common serious adverse reactions reported to occur with fentanyl are respiratory depression, apnea, rigidity and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypertension, hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, diaphoresis, serotonin syndrome, adrenal insufficiency, and anaphylaxis.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. When a tranquilizer is used with Fentanyl Citrate Injection, the following adverse reactions can occur: chills and/or shivering, restlessness and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of neuroleptics with fentanyl citrate.

Cases of cardiac dysrhythmias, cardiac arrest, and death have been reported following the use of fentanyl citrate with a neuroleptic agent.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

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

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in Fentanyl Citrate Injection

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology]*.

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

DRUG INTERACTIONS
Clinically Significant Drug Interactions with Fentanyl Citrate Injection

Inhibitors of CYP3A4	
Clinical Impact:	The concomitant use of Fentanyl Citrate Injection and CYP3A4 inhibitors can increase the plasma concentration of fentanyl, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of Fentanyl Citrate Injection is achieved *[see Warnings and Precautions]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl plasma concentration will decrease *[see Clinical Pharmacology]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to fentanyl.
Intervention:	If concomitant use is necessary, consider dosage reduction of Fentanyl Citrate Injection until stable drug effects are achieved *[see Dosage and Administration]*. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the Fentanyl Citrate Injection dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir), grapefruit juice
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of Fentanyl Citrate Injection and CYP3A4 inducers can decrease the plasma concentration of fentanyl *[see Clinical Pharmacology]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to fentanyl *[see Warnings and Precautions]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase *[see Clinical Pharmacology]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the Fentanyl Citrate Injection dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider Fentanyl Citrate Injection dosage reduction and monitor for signs of respiratory depression.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	The concomitant use of Fentanyl Citrate Injection with CNS depressants my result in decreased pulmonary artery pressure and may cause hypotension. Even small dosages of diazepam may cause cardiovascular depression when added to high dose or anesthetic dosages of Fentanyl Citrate Injection. As postoperative analgesia, concomitant use of Fentanyl Citrate Injection can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	As postoperative analgesia, start with a lower dose of Fentanyl Citrate Injection and monitor patients for signs of respiratory depression, sedation, and hypotension. Fluids or other measures to counter hypotension should be available *[see Warnings and Precautions]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, barbiturates, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Warnings and Precautions]*.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Fentanyl Citrate Injection if serotonin syndrome is suspected.

Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome *[see Warnings and Precautions]* or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions]*
Intervention:	The use of Fentanyl Citrate Injection is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	Phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of Fentanyl Citrate Injection and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	Butorphanol, nalbuphine, pentazocine, buprenorphine.
Muscle Relaxants	
Clinical Impact:	Fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Fentanyl Citrate Injection and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when Fentanyl Citrate Injection is used concomitantly with anticholinergic drugs.
Neuroleptics	
Clinical Impact:	Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of Fentanyl Citrate Injection combined with a neuroleptic *[see Warnings and Precautions].*
Intervention:	ECG monitoring is indicated when a neuroleptic agent is used in conjunction with Fentanyl Citrate Injection as an anesthetic premedication, for the induction of anesthesia, or as an adjunct in the maintenance of general or regional anesthesia.
Nitrous oxide	
Clinical Impact:	Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of Fentanyl Citrate Injection.
Intervention:	Monitor patients for signs of cardiovascular depression that may be greater than otherwise expected.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with Fentanyl Citrate Injection in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, fentanyl administration to pregnant rats during organogenesis was embryocidal at doses within the range of the human recommended dosing. No evidence of malformations was noted in animal studies completed to date *[see Data]*.

The estimated 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

Prolonged use of opioid analgesics 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.

Labor or Delivery

There are insufficient data to support the use of fentanyl in labor or delivery. Therefore, such use is not recommended. 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. Fentanyl Citrate Injection is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including Fentanyl Citrate Injection, can prolong labor through actions which 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 dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data

Fentanyl has been shown to embryocidal in pregnant rats at doses of 30 mcg/kg intravenously (0.05 times the human dose of 100 mcg/kg on a mg/m2 basis) and 160 mcg/kg subcutaneously (0.26 times the human dose of 100 mcg/kg on a mg/m2 basis). There was no evidence of teratogenicity reported.

No evidence of malformations or adverse effects on the fetus was reported in a published study in which pregnant rats were administered fentanyl continuously via subcutaneously implanted osmotic minipumps at doses of 10, 100, or 500 mcg/kg/day starting 2-weeks prior to breeding and throughout pregnancy. The high dose was approximately 0.81 times the human dose of 100 mcg/kg on a mg/m2 basis.

Lactation

Risk Summary

Fentanyl is present in breast milk. One published lactation study reports a relative infant dose of fentanyl of 0.38%. However, there is insufficient information to determine the effects of fentanyl on the breastfed infant and the effects of fentanyl on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Fentanyl Citrate Injection and any potential adverse effects on the breastfed infant from Fentanyl Citrate Injection or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to fentanyl through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

Females and Males of Reproductive Potential

Infertility

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 *[see Adverse Reactions, Clinical Pharmacology, Nonclinical Toxicology]*.

Pediatric Use

The safety and efficacy of Fentanyl Citrate Injection in pediatric patients under two years of age has not been established.

Rare cases of unexplained clinically significant methemoglobinemia have been reported in premature neonates undergoing emergency anesthesia and surgery which included combined use of fentanyl, pancuronium and atropine. A direct cause and effect relationship between the combined use of these drugs and the reported cases of methemoglobinemia has not been established.

Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to fentanyl. 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 Fentanyl Citrate Injection slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions]*.

Fentanyl 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

Fentanyl Citrate Injection should be administered with caution to patients with liver dysfunction because of the extensive hepatic metabolism. Reduce the dosage as needed and monitor closely for signs of respiratory depression, sedation, and hypotension.

Renal Impairment

Fentanyl Citrate Injection should be administered with caution to patients with kidney dysfunction because of the renal excretion of Fentanyl Citrate Injection and its metabolites. Reduce the dosage as needed and monitor closely for signs of respiratory depression, sedation, and hypotension.

OVERDOSAGE

Clinical Presentation

Acute overdose with Fentanyl Citrate 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 *[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 measured (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. For clinically significant respiratory or circulatory depression secondary to fentanyl overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to opioid overdose. Because the duration of opioid reversal is expected to be less than the duration of action of fentanyl in Fentanyl Citrate Injection, carefully monitor the patient until spontaneous respiration is reliably re-established. 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.

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 initiated with care and by titration with smaller than usual doses of the antagonist.

Simplist® 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 opiod 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 uticaria, 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 affectedy 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.

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Simplist® 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 absence of resuscitative equipment *[see Warnings and Precautions]*.
- Concurrent use of mon oamine 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, lifethreatening 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, option 5, 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 reversal of 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.

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