

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DILAUID® INJECTION safely and effectively.

See full prescribing information for DILAUID® INJECTION.

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

Initial U.S. Approval: January 1984

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. (5.1)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.2)
- 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. (5.3)
- 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. (5.4, 7).

| RECENT MAJOR CHANGES | |
|--|----------------|
| Boxed Warning, information pertaining to the discontinued product DILAUID-DP | Removed 1/2018 |
| Indications and Usage, information pertaining to DILAUID-DP (1) | Removed 1/2018 |
| Dosage and Administration, information pertaining to DILAUID-DP (2) | Removed 1/2018 |
| Contraindications, information pertaining to DILAUID-DP (4) | Removed 1/2018 |
| Warnings and Precautions, information pertaining to DILAUID-DP (5) | Removed 1/2018 |

INDICATIONS AND USAGE

DILAUID 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. (1)

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

DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)

Initial Dosage:

- Intramuscular or Subcutaneous Use:* The usual starting dose is 1 mg to 2 mg every 2 to 3 hours as necessary. (2.2)
- Intravenous Use:* The usual starting dose is 0.2 mg to 1 mg every 2 to 3 hours. The injection should be given slowly, over at least 2 to 3 minutes. (2.2)

FULL PRESCRIBING INFORMATION: CONTENTS*

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

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
 - Important Dosage and Administration Instructions
 - Initial Dosage
 - Dosage Modifications in Patients with Hepatic Impairment
 - Dosage Modifications in Patients with Renal Impairment
 - Titration and Maintenance of Therapy
 - Discontinuation of DILAUID INJECTION
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
 - Addiction, Abuse, and Misuse
 - Life-Threatening Respiratory Depression
 - Neonatal Opioid Withdrawal Syndrome
 - Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants
 - Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients
 - Adrenal Insufficiency
 - Severe Hypotension
 - Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness
 - Risks of Use in Patients with Gastrointestinal Conditions
 - Increased Risk of Seizures in Patients with Seizure Disorders
 - Withdrawal
 - Risks of Driving and Operating Machinery
 - Sulfites
 - Increased Risk of Hypotension and Respiratory Depression with Rapid Intravenous Administration

FULL PRESCRIBING 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

Addiction, Abuse, and Misuse

DILAUID 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 DILAUID INJECTION and monitor all patients regularly for the development of these behaviors and conditions [see *Warnings and Precautions* (5.1)].

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of DILAUID INJECTION. Monitor for respiratory depression, especially during initiation of DILAUID INJECTION or following a dose increase [see *Warnings and Precautions* (5.2)].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of DILAUID 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* (5.3)].

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* (5.4), *Drug Interactions* (7)].

- Reserve concomitant prescribing of DILAUID 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.

- Hepatic Impairment:** Initiate treatment with one-fourth to one-half the usual starting dose, depending on degree of hepatic impairment. (2.3)
- Renal Impairment:** Initiate treatment with one-fourth to one-half the usual starting dose, depending on degree of renal impairment. (2.4)
- Do not stop DILAUID INJECTION abruptly in a physically-dependent patient. (2.6)

DOSAGE FORMS AND STRENGTHS

- DILAUID Injection, 0.5 mg/0.5 mL, 1 mg/mL or 2 mg/mL, are available in pre-filled, disposable syringes. (3)

CONTRAINDICATIONS

- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Known hypersensitivity to hydromorphone, hydromorphone salts, sulfite-containing medications, or any other components of the product (4)

WARNINGS AND PRECAUTIONS

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients:** Monitor closely, particularly during initiation and titration. (5.5)
- Adrenal Insufficiency:** If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.6)
- Severe Hypotension:** Monitor during dosage initiation and titration. Avoid use of DILAUID INJECTION in patients with circulatory shock. (5.7)
- 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 DILAUID INJECTION in patients with impaired consciousness or coma. (5.8)
- DILAUID INJECTION contains sodium metabisulfite. There is a risk of anaphylactic symptoms and life-threatening asthmatic episodes in susceptible people (5.13)

ADVERSE REACTIONS

Most common adverse reactions are lightheadedness, dizziness, sedation, nausea, vomiting, sweating, flushing, dysphoria, euphoria, dry mouth, and pruritus. (6)

To report Suspected Adverse Reactions, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Serotonergic Drugs:** Concomitant use may result in serotonin syndrome. Discontinue DILAUID INJECTION if serotonin syndrome is suspected. (7)
- 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. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics:** Avoid use with DILAUID INJECTION because they may reduce analgesic effect of DILAUID INJECTION or precipitate withdrawal symptoms. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2018

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- Pregnancy
- Lactation
- Females and Males of Reproductive Potential
- Pediatric Use
- Geriatric Use
- Hepatic Impairment
- Renal Impairment

9 DRUG ABUSE AND DEPENDENCE

- Controlled Substance
- Abuse
- Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- Mechanism of Action
- Pharmacodynamics
- Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

1 INDICATIONS AND USAGE

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 [see *Warnings and Precautions* (5.1)], 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, or are not expected to be tolerated
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see *Warnings and Precautions* (5)].

- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see *Warnings and Precautions* (5.1)].

- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with DILAUID INJECTION and adjust the dosage accordingly [see *Warnings and Precautions* (5.2)].
- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit. A slight yellowish discoloration may develop in DILAUID INJECTION. No loss of potency has been demonstrated. DILAUID INJECTION is physically compatible and chemically stable for at least 24 hours at 25°C, protected from light in most common large-volume parenteral solutions.

- Discard any unused portion in an appropriate manner.

2.2 Initial Dosage

Use of DILAUID INJECTION as the First Opioid Analgesic:

Subcutaneous or Intramuscular Administration:

The usual starting dose of DILAUID INJECTION is 1 mg to 2 mg every 2 to 3 hours as necessary. Depending on the clinical situation, the initial starting dose may be lowered in patients who are opioid naïve.

Intravenous Administration:

The initial starting dose is 0.2 to 1 mg every 2 to 3 hours. Intravenous administration should be given slowly, over at least 2 to 3 minutes, depending on the dose. The initial dose should be reduced in the elderly or debilitated and may be lowered to 0.2 mg.

Conversion From Other Opioids to DILAUID INJECTION:

There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of DILAUID INJECTION. It is safer to underestimate a patient's 24-hour DILAUID INJECTION dosage than to overestimate the 24-hour DILAUID INJECTION dosage and manage an adverse reaction due to overdose.

If the decision is made to convert to Hydromorphone Hydrochloride Injection from another opioid analgesic using publicly available data, convert the current total daily amount(s) of opioid(s) received to an equivalent total daily dose of DILAUID INJECTION and reduce by one-half due to the possibility of incomplete cross tolerance. Divide the new total amount by the number of doses permitted based on dosing interval (e.g., 8 doses for every-three-hour dosing). Titrate the dose according to the patient's response.

2.3 Dosage Modifications in Patients with Hepatic Impairment

Start patients with hepatic impairment on one-fourth to one-half the usual DILAUID INJECTION starting dose depending on the extent of impairment [see *Clinical Pharmacology* (12.3)].

2.4 Dosage Modifications in Patients with Renal Impairment

Start patients with renal impairment on one-fourth to one-half the usual DILAUID INJECTION starting dose depending on the degree of impairment [see *Clinical Pharmacology* (12.3)].

2.5 Titration and Maintenance of Therapy

Individually titrate DILAUID INJECTION to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving DILAUID INJECTION to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [see *Warnings and Precautions* (5.1)]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the DILAUID INJECTION dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.6 Discontinuation of DILAUID INJECTION

When a patient who has been taking DILAUID INJECTION regularly and may be physically dependent no longer requires therapy with DILAUID INJECTION, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue DILAUID INJECTION in a physically-dependent patient [see *Warnings and Precautions* (5.11), *Drug Abuse and Dependence* (9.3)].

DOSAGE FORMS AND STRENGTHS

DILAUID INJECTION:

Each pre-filled syringe contains 0.5 mg/0.5 mL, 1 mg/mL or 2 mg/mL of hydromorphone hydrochloride in a sterile, aqueous solution.

CONTRAINDICATIONS

DILAUID INJECTION is contraindicated in patients with:

- Significant respiratory depression [see *Warnings and Precautions* (5.2)]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see *Warnings and Precautions* (5.2)]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see *Warnings and Precautions* (5.9)]
- Hypersensitivity to hydromorphone, hydromorphone salts, any other components of the product, or sulfite containing medications (e.g., anaphylaxis) [see *Warnings and Precautions* (5.13)]

WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

DILAUID INJECTION contains hydromorphone, a Schedule II controlled substance. As an opioid, DILAUID INJECTION exposes users to the risks of addiction, abuse, and misuse [see *Drug Abuse and Dependence* (9)].

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

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

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing DILAUID INJECTION. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 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. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see *Overdosage* (10)]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of DILAUID INJECTION, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of DILAUID INJECTION.

To reduce the risk of respiratory depression, proper dosing and titration of DILAUID INJECTION is essential [see *Dosage and Administration* (2)]. Overestimating the DILAUID INJECTION dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of DILAUID INJECTION during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Use in Specific Populations* (8.1), *Patient Counseling Information* (17)].

5.4 Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

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

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see *Drug Interactions* (7)].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Psychiatric disorders: agitation, mood altered, nervousness, anxiety, depression, hallucination, disorientation, insomnia, abnormal dreams

Renal and urinary disorders: urinary retention, urinary hesitancy, antidiuretic effects

Reproductive system and breast disorders: erectile dysfunction

Respiratory, thoracic, and mediastinal disorders: bronchospasm, laryngospasm, dyspnea, oropharyngeal swelling

Skin and subcutaneous tissue disorders: injection site pain, urticaria, rash, hyperhidrosis

Vascular disorders: flushing, hypotension, hypertension

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

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

Patients with Chronic Pulmonary Disease: DILAUID INJECTION treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of DILAUID INJECTION [see *Warnings and Precautions* (5.2)].

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see *Warnings and Precautions* (5.2)].

Monitor such patients closely, particularly when initiating and titrating DILAUID INJECTION and when DILAUID INJECTION is given concomitantly with other drugs that depress respiration [see *Warnings and Precautions* (5.2)]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.6 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.

5.7 Severe Hypotension

DILAUID INJECTION may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) [see *Drug Interactions* (7)]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of DILAUID INJECTION. In patients with circulatory shock, DILAUID INJECTION may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of DILAUID INJECTION in patients with circulatory shock.

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

In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), DILAUID INJECTION may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with DILAUID INJECTION.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of DILAUID INJECTION in patients with impaired consciousness or coma.

5.9 Risks of Use in Patients with Gastrointestinal Conditions

DILAUID INJECTION is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. The hydromorphone in DILAUID 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.

5.10 Increased Risk of Seizures in Patients with Seizure Disorders

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

5.11 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including DILAUID INJECTION. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms [see *Drug Interactions* (7)].

When discontinuing DILAUID INJECTION in a physically-dependent patient, gradually taper the dosage [see *Dosage and Administration* (2.6)]. Do not abruptly discontinue DILAUID INJECTION in these patients [see *Drug Abuse and Dependence* (9.3)].

5.12 Risks of Driving and Operating Machinery

DILAUID 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 DILAUID INJECTION and know how they will react to the medication [see *Patient Counseling Information* (17)].

5.13 Sulfites

DILAUID INJECTION contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

5.14 Increased Risk of Hypotension and Respiratory Depression with Rapid Intravenous Administration

DILAUID INJECTION may be given intravenously, but the injection should be given very slowly. Rapid intravenous injection of opioid analgesics increases the possibility of side effects such as hypotension and respiratory depression [see *Dosage and Administration* (2)].

6 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* (5.1)]
- Life-Threatening Respiratory Depression [see *Warnings and Precautions* (5.2)]
- Neonatal Opioid Withdrawal Syndrome [see *Warnings and Precautions* (5.3)]
- Interactions with Benzodiazepines and Other CNS Depressants [see *Warnings and Precautions* (5.4)]
- Adrenal Insufficiency [see *Warnings and Precautions* (5.6)]
- Severe Hypotension [see *Warnings and Precautions* (5.7)]
- Gastrointestinal Adverse Reactions [see *Warnings and Precautions* (5.9)]
- Seizures [see *Warnings and Precautions* (5.10)]
- Withdrawal [see *Warnings and Precautions* (5.11)]

The following adverse reactions associated with the use of hydromorphone 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.

Serious adverse reactions associated with DILAUID INJECTION include respiratory depression and apnea and, to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest.

The most common adverse effects are lightheadedness, dizziness, sedation, nausea, vomiting, sweating, flushing, dysphoria, euphoria, dry mouth, and pruritus. These effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain.

In a published study, neural tube defects (encephalocele and craniochisis) were noted following subcutaneous administration of hydromorphone hydrochloride (19 to 258 mg/kg) on Gestation Day 9 to pregnant hamsters (6.4 to 87.2 times the HDD of 24 mg/kg/day based on body surface area). The findings cannot be clearly attributed to maternal toxicity. No neural tube defects were noted at 14 mg/kg (4.7 times the human daily dose of 24 mg/kg/day).

In a published study, CF-1 mice were treated subcutaneously with continuous infusion of 7.5, 15, or 30 mg/kg/day hydromorphone hydrochloride (1.5, 3, or 6.1 times the human daily dose of 24 mg based on body surface area) via implanted osmotic pumps during organogenesis (Gestation Days 7 to 10). Soft tissue malformations (cryptorchidism, cleft palate, malformed ventricles and retina), and skeletal variations (split supraoccipital, checkerboard and split sternalbrae, delayed ossification of the paws and ectopic ossification sites) were observed at doses 3 times the human dose of 24 mg/kg/day based on body surface area. The findings cannot be clearly attributed to maternal toxicity.

Increased pup mortality and decreased pup body weights were noted at 0.8 and 2 times the human daily dose of 24 mg in a study in which pregnant rats were treated with hydromorphone hydrochloride from Gestation Day 7 to Lactation Day 20 via oral gavage doses of 0, 0.5, 2, or 5 mg/kg/day (0.2, 0.8, or 2 times the HDD of 24 mg based on body surface area, respectively). Maternal toxicity (decreased food consumption and body weight gain) was also noted at the two highest doses tested.

8.2 Lactation

Risk Summary

Low levels of opioid analgesics have been detected in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for DILAUDID INJECTION and any potential adverse effects on the breastfed infant from DILAUDID INJECTION or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to DILAUDID INJECTION through breast milk 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.

8.3 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* (6), *Clinical Pharmacology* (12.2), *Nonclinical Toxicology* (13.1)].

8.4 Pediatric Use

The safety and effectiveness of DILAUDID INJECTION in pediatric patients has not been established.

8.5 Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to hydromorphone. 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 DILAUDID INJECTION slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see *Warnings and Precautions* (5.5)].

Hydromorphone 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.

8.6 Hepatic Impairment

The pharmacokinetics of hydromorphone are affected by hepatic impairment. Due to increased exposure of hydromorphone, patients with moderate hepatic impairment should be started at one-fourth to one-half the recommended starting dose depending on the degree of hepatic dysfunction and closely monitored during dose titration. The pharmacokinetics of hydromorphone in patients with severe hepatic impairment has not been studied. A further increase in C_{max} and AUC of hydromorphone in this group is expected and should be taken into consideration when selecting a starting dose [see *Clinical Pharmacology* (12.3)].

8.7 Renal Impairment

The pharmacokinetics of hydromorphone are affected by renal impairment. Start patients with renal impairment on one-fourth to one-half the usual starting dose depending on the degree of impairment. Patients with renal impairment should be closely monitored during dose titration [see *Clinical Pharmacology* (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

DILAUDID INJECTION contains hydromorphone, which is a Schedule II controlled substance.

9.2 Abuse

DILAUDID INJECTION contains hydromorphone hydrochloride, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. DILAUDID INJECTION can be abused and is subject to misuse, addiction, and criminal diversion [see *Warnings and Precautions* (5.1)].

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include, emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering of prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare providers. “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

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

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

Risks Specific to Abuse of DILAUDID INJECTION

Abuse of DILAUDID INJECTION poses a risk of overdose and death. The risk is increased with concurrent use of DILAUDID INJECTION with alcohol and other central nervous system depressants.

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

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation of a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

DILAUDID INJECTION should not be abruptly discontinued in a physically-dependent patient [see *Dosage and Administration* (2.6)]. If DILAUDID INJECTION is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see *Use in Specific Populations* (8.1)].

10 OVERDOSAGE

Clinical Presentation

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 [see *Clinical Pharmacology* (12.2)].

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent airway 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. For clinically significant respiratory or circulatory depression secondary to hydromorphone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to hydromorphone overdose.

Because the duration of opioid reversal is expected to be less than the duration of hydromorphone in DILAUDID INJECTION, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product’s prescribing information.

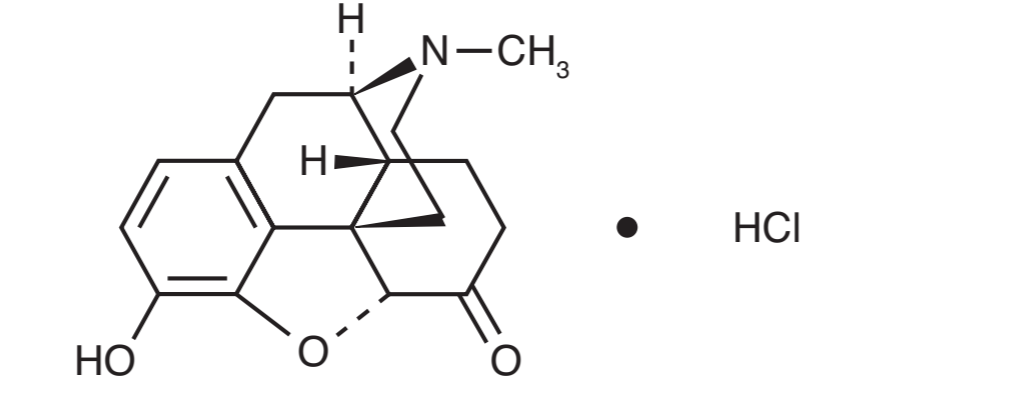
In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. 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.

11 DESCRIPTION

DILAUDID (hydromorphone hydrochloride), a hydrogenated ketone of morphine, is an opioid agonist.

DILAUDID INJECTION is available as a sterile, aqueous solution in clear and colorless pre-filled syringes for slow intravenous, subcutaneous, or intramuscular administration. Each 1 mL of solution contains 1 mg or 2 mg of hydromorphone hydrochloride.

The chemical name of DILAUDID is 4,5α-epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride. The molecular weight is 321.80. Its molecular formula is C₁₇H₁₉NO₃·HCl, and it has the following chemical structure:



Hydromorphone hydrochloride is a white or almost white crystalline powder that is freely soluble in water, very slightly soluble in ethanol (96%), and practically insoluble in methylene chloride.

The inactive ingredients in DILAUDID (hydromorphone hydrochloride) include: 0.2% sodium citrate and 0.2% citric acid added as a buffer to maintain a pH between 3.5 and 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

Effects on the Central Nervous System

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

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

Effects on the Gastrointestinal Tract and Other Smooth Muscle

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

Effects on the Cardiovascular System

Hydromorphone produces peripheral vasodilation which may result in orthostatic hypotension or syncope, manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, and sweating and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [see *Adverse Reactions* (6)]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see *Adverse Reactions* (6)].

Effects on the Immune System

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

Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of hydromorphone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance [see *Dosage and Administration* (2.1, 2.2)].

Concentration–Adverse Reaction Relationships

There is a relationship between increasing hydromorphone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [see *Dosage and Administration* (2.1, 2.2)].

12.3 Pharmacokinetics

Distribution

At therapeutic plasma levels, hydromorphone is approximately 8-19% bound to plasma proteins. After an intravenous bolus dose, the steady state of volume of distribution [mean (±CV)] is 302.9 (32%) liters.

Elimination

The systemic clearance is approximately 1.96 (20%) liters/minute. The terminal elimination half-life of hydromorphone after an intravenous dose is about 2.3 hours.

Metabolism

Hydromorphone is extensively metabolized via glucuronidation in the liver, with greater than 95% of the dose metabolized to hydromorphone-3-glucuronide along with minor amounts of 6-hydroxy reduction metabolites.

Excretion

Only a small amount of the hydromorphone dose is excreted unchanged in the urine. Most of the dose is excreted as hydromorphone-3-glucuronide along with minor amounts of 6-hydroxy reduction metabolites.

Special Populations

Hepatic Impairment

After oral administration of hydromorphone at a single 4 mg dose (2 mg hydromorphone immediate-release tablets), mean exposure to hydromorphone (C_{max} and AUC_∞) is increased 4-fold in patients with moderate (Child-Pugh Group B) hepatic impairment compared with subjects with normal hepatic function. Patients with moderate hepatic impairment should

be started at one-fourth to one-half the recommended starting dose and closely monitored during dose titration. The pharmacokinetics of hydromorphone in patients with severe hepatic impairment has not been determined. A further increase in C_{max} and AUC of hydromorphone in this group is expected and should be taken into consideration when selecting a starting dose [see *Use in Specific Populations* (8.6)].

Renal Impairment

The pharmacokinetics of hydromorphone following an oral administration of hydromorphone at a single 4 mg dose (2 mg hydromorphone immediate-release tablets) are affected by renal impairment. Mean exposure to hydromorphone (C_{max} and AUC_∞) is increased by 2-fold in patients with moderate (CL_{cr} = 40–60 mL/min) renal impairment and increased by 4-fold in patients with severe (CL_{cr}< 30 mL/min) renal impairment compared with normal subjects (CL_{cr}> 80 mL/min). In addition, in patients with severe renal impairment, hydromorphone appeared to be more slowly eliminated with a longer terminal elimination half-life (40 hr) compared to patients with normal renal function (15 hr). Start patients with renal impairment on one-fourth to one-half the usual starting dose depending on the degree of impairment. Patients with renal impairment should be closely monitored during dose titration [see *Use in Specific Populations* (8.7)].

Geriatric Population

In the geriatric population, age has no effect on the pharmacokinetics of hydromorphone.

Sex

Sex has little effect on the pharmacokinetics of hydromorphone. Females appear to have a higher C_{max} (25%) than males with comparable AUC₀₋₂₄ values. The difference observed in C_{max} may not be clinically relevant.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

Hydromorphone was positive in the mouse lymphoma assay in the presence of metabolic activation, but was negative in the mouse lymphoma assay in the absence of metabolic activation. Hydromorphone was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames assay). Hydromorphone was not clastogenic in either the *in vitro* human lymphocyte chromosome aberration assay or the *in vivo* mouse micronucleus assay.

Impairment of Fertility

Reduced implantation sites and viable fetuses were noted at 2.1 times the human daily dose of 32 mg/day in a study in which female rats were treated orally with 1.75, 3.5, or 7 mg/kg/day hydromorphone hydrochloride (0.5, 1.1, or 2.1 times a human daily dose of 24 mg/day (HDD) based on body surface area) beginning 14 days prior to mating through Gestation Day 7 and male rats were treated with the same hydromorphone hydrochloride doses beginning 28 days prior to and throughout mating.

16 HOW SUPPLIED/STORAGE AND HANDLING

DILAUDID INJECTION (hydromorphone hydrochloride) is supplied in clear and colorless pre-filled syringes. Each pre-filled syringe of sterile, aqueous solution contains 0.5 mg, 1 mg or 2 mg hydromorphone hydrochloride with 0.2% sodium citrate and 0.2% citric acid solution. DILAUDID INJECTION contains no added preservative and is supplied as follows:

0.5 mg/0.5 mL pre-filled disposable syringe, NDC 76045-009-05

1 mg/mL pre-filled disposable syringe, NDC 76045-009-10

2 mg/mL pre-filled disposable syringe, NDC 76045-010-10

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

PROTECT FROM LIGHT.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Safety and Handling Instructions

Access to drugs with a potential for abuse such as DILAUDID INJECTION presents an occupational hazard for addiction in the health care industry. Routine procedures for handling controlled substances developed to protect the public may not be adequate to protect health care workers. Implementation of more effective accounting procedures and measures to restrict access to drugs of this class (appropriate to the practice setting) may minimize the risk of self-administration by health care providers.

17 PATIENT COUNSELING INFORMATION

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications. [see *Drug Interactions* (7)].

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [see *Adverse Reactions* (6)].

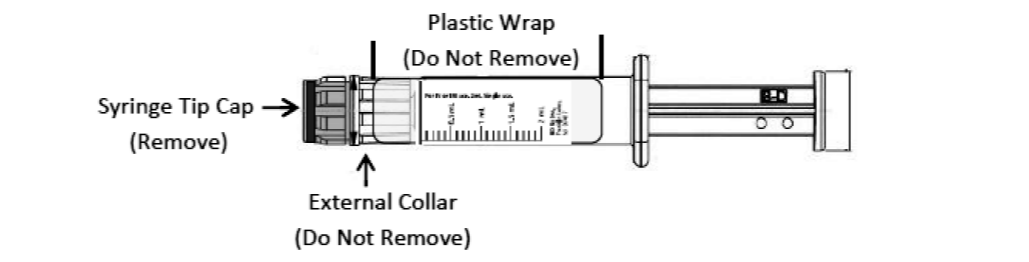
Healthcare professionals can telephone Fresenius Kabi USA, LLC at 1-800-551-7176 for information or to report adverse events on this product.

INSTRUCTIONS FOR USE

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

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

Figure 1



1. Inspect the outer packaging (blister pack) by verifying:

- blister integrity
- drug name
- drug strength
- dose volume
- route of administration
- expiry date to be sure that the drug has not expired
- sterile field applicability

Do not use if package has been damaged.

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

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

Figure 2



4. Perform visual inspection on the syringe by verifying:

- absence of syringe damage
- absence of external particles
- absence of internal particles
- proper drug color
- expiration date to be sure that the drug has not expired
- drug name
- drug strength
- dose volume
- route of administration
- integrity of the plastic wrap around the external collar

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

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

Figure 3



Figure 4

Figure 5

Figure 6

Figure 7

Figure 8

Figure 9

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

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

12. Remove syringe from NLAD (if applicable) and discard into appropriate receptacle. If delivering the medication with a needle, to prevent needle stick injuries, do not recap needle.

NOTES:

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

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

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



Lake Zurich, IL 60047

www.fresenius-kabi.com/us

Rev. 1/2018

451535C

Dilaudid is a licensed trademark of Purdue Pharma LP.