

**DILAUDID- hydromorphone hydrochloride tablet**  
**DILAUDID- hydromorphone hydrochloride solution**  
**Rhodes Pharmaceuticals L.P.**

-----

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use DILAUDID® ORAL SOLUTION and DILAUDID® TABLETS safely and effectively. See full prescribing information for DILAUDID® ORAL SOLUTION and DILAUDID® TABLETS.

DILAUDID® (hydromorphone hydrochloride) oral solution

DILAUDID® (hydromorphone hydrochloride) tablets, for oral use, CII

Initial U.S. Approval: January 1984

**WARNING: RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS**

*See full prescribing information for complete boxed warning.*

- Ensure accuracy when prescribing, dispensing, and administering DILAUDID Oral Solution. Dosing errors due to confusion between mg and mL can result in accidental overdose and death. (2.1, 5.1)
- DILAUDID Oral Solution or DILAUDID Tablets 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. (5.2)
- To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.3)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.4)
- Accidental ingestion of DILAUDID Oral Solution or DILAUDID Tablets, especially by children, can result in a fatal overdose of hydromorphone. (5.4)
- Prolonged use of DILAUDID Oral Solution or DILAUDID Tablets 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. (5.5)
- 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. (5.6, 7).

----- **RECENT MAJOR CHANGES** -----

Dosage and Administration (2.2)

03/2021

Warnings and Precautions (5.2, 5.4, 5.6)

03/2021

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

DILAUDID Oral Solution and DILAUDID Tablets contain hydromorphone, an opioid agonist, and are indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

Limitations of Use (1)

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve DILAUDID Oral Solution or DILAUDID Tablets 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)
- Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with DILAUDID Oral Solution or DILAUDID Tablets. Consider prescribing naloxone based on the patient's risk factors for overdose. (2.2, 5.2, 5.4, 5.6)
- Usual adult dosage of DILAUDID Oral Solution is one-half (2.5 mL) to two teaspoonsful (10 mL), 2.5 mg to 10 mg, every 3 to 6 hours. (2.3)
- Usual adult starting dose for DILAUDID Tablets is 2 mg to 4 mg, orally, every 4 to 6 hours. (2.3)
- Hepatic Impairment: Initiate treatment with one-fourth to one-half the usual starting dose, depending on degree of hepatic impairment. (2.4)
- Renal Impairment: Initiate treatment with one-fourth to one-half the usual starting dose, depending on degree of renal impairment. (2.5)
- Do not abruptly discontinue DILAUDID Oral Solution or DILAUDID Tablets in a physically-dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.7)

### ----- **DOSAGE FORMS AND STRENGTHS** -----

- DILAUDID Oral Solution: 5 mg/5 mL (1 mg/mL)
- DILAUDID Tablets: 2 mg, 4 mg, 8 mg (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, or sulfite-containing medications (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. (5.7)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.8)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of DILAUDID Oral Solution or DILAUDID Tablets in patients with circulatory shock. (5.9)
- 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 Oral Solution or DILAUDID Tablets in patients with impaired consciousness or coma. (5.10)

### ----- **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 Rhodes Pharmaceuticals L.P. at 1-888-827-0616 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**

### ----- **DRUG INTERACTIONS** -----

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue DILAUDID Oral Solution or DILAUDID Tablets 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 DILAUDID because they may reduce analgesic effect of DILAUDID or precipitate withdrawal symptoms. (7)

### ----- **USE IN SPECIFIC POPULATIONS** -----

- Pregnancy: May cause fetal harm. (8.1)

---

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**WARNING: RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS**

**1 INDICATIONS AND USAGE**

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Important Dosage and Administration Instructions
- 2.2 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose
- 2.3 Initial Dosage
- 2.4 Dosage Modifications in Patients with Hepatic Impairment
- 2.5 Dosage Modifications in Patients with Renal Impairment
- 2.6 Titration and Maintenance of Therapy
- 2.7 Safe Reduction or Discontinuation of DILAUDID Oral Solution or DILAUDID Tablets

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Risk of Accidental Overdose and Death due to Medication Errors
- 5.2 Addiction, Abuse, and Misuse
- 5.3 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
- 5.4 Life-Threatening Respiratory Depression
- 5.5 Neonatal Opioid Withdrawal Syndrome
- 5.6 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants
- 5.7 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients
- 5.8 Adrenal Insufficiency
- 5.9 Severe Hypotension
- 5.10 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness
- 5.11 Risks of Use in Patients with Gastrointestinal Conditions
- 5.12 Increased Risk of Seizures in Patients with Seizure Disorders
- 5.13 Withdrawal
- 5.14 Risks of Driving and Operating Machinery
- 5.15 Sulfites

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trial Experience
- 6.2 Postmarketing Experience

**7 DRUG INTERACTIONS**

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.2 Lactation

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

8.7 Renal Impairment

**9 DRUG ABUSE AND DEPENDENCE**

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

**10 OVERDOSAGE**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

**13 NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**14 CLINICAL STUDIES**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

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

---

**FULL PRESCRIBING INFORMATION**

**WARNING: RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS**

**Risk of Medication Errors**

Ensure accuracy when prescribing, dispensing, and administering DILAUDID Oral Solution. Dosing errors due to confusion between mg and mL can result in accidental overdose and death [see *Dosage and Administration (2.1), Warnings and Precautions (5.1)*].

**Addiction, Abuse, and Misuse**

DILAUDID Oral Solution and DILAUDID Tablets expose 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 Oral Solution or DILAUDID Tablets, and monitor all patients regularly for the development of these behaviors and conditions [see *Warnings and Precautions (5.2)*].

**Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)**

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products [see *Warnings and Precautions (5.3)*]. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

**Life-Threatening Respiratory Depression**

Serious, life-threatening, or fatal respiratory depression may occur with use of DILAUDID Oral Solution and DILAUDID Tablets. Monitor for respiratory depression, especially during initiation of DILAUDID Oral Solution or DILAUDID Tablets or following a dose increase [see *Warnings and Precautions (5.4)*].

**Accidental Ingestion**

Accidental ingestion of even one dose of DILAUDID Oral Solution or DILAUDID Tablets, especially by children, can result in a fatal overdose of hydromorphone [see *Warnings and Precautions (5.4)*].

## **Neonatal Opioid Withdrawal Syndrome**

**Prolonged use of DILAUDID Oral Solution or DILAUDID Tablets 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 (5.5)*].**

## **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 (5.6)*, *Drug Interactions (7)*].**

- **Reserve concomitant prescribing of DILAUDID Oral Solution OR DILAUDID Tablets 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.**

## **1 INDICATIONS AND USAGE**

DILAUDID Oral Solution and DILAUDID Tablets are 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 (5.2)*], reserve DILAUDID Oral Solution and DILAUDID Tablets 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

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Important Dosage and Administration Instructions**

Ensure accuracy when prescribing, dispensing, and administering DILAUDID Oral Solution to avoid dosing errors due to confusion between mg and mL, which could result in accidental overdose and death. Ensure the proper dose is communicated and dispensed. When writing prescriptions, include both the total dose in mg and the total

dose in volume.

Instruct patients to obtain a calibrated measuring cup/syringe for administering DILAUDID Oral Solution to ensure that the dose is measured and administered accurately.

Do not use household teaspoons or tablespoons to measure DILAUDID Oral Solution, as using a tablespoon instead of a teaspoon could lead to overdosage [see *Warnings and Precautions (5.1)*].

- 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 (5.2)*].
- Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with DILAUDID Oral Solution or DILAUDID Tablets and adjust the dosage accordingly [see *Warnings and Precautions (5.4)*].

## **2.2 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose**

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with DILAUDID Oral Solution or DILAUDID Tablets [see *Warnings and Precautions (5.4)*, *Patient Counseling Information (17)*].

Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient [see *Warnings and Precautions (5.2, 5.4, 5.6)*].

Consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.

## **2.3 Initial Dosage**

### Initiating Treatment with DILAUDID Oral Solution or DILAUDID Tablets

#### *Dilaudid Oral Solution*

Initiate treatment with DILAUDID Oral Solution in a dosing range of one-half (2.5 mL) to two teaspoonsful (10 mL), 2.5 mg to 10 mg, every 3 to 6 hours as needed for pain.

#### *Dilaudid Tablets*

Initiate treatment with DILAUDID Tablets in a dosing range of 2 mg to 4 mg, orally, every 4 to 6 hours.

### Conversion from Other Opioids to DILAUDID Oral Solution or DILAUDID Tablets

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 DILAUDID Oral Solution or DILAUDID Tablets. It is safer to underestimate a patient's 24-hour DILAUDID dosage than to overestimate the 24-hour dosage and manage an adverse reaction due to overdose.

In general, it is safest to start DILAUDID therapy by administering half of the usual starting dose every 3 to 6 hours for DILAUDID Oral Solution; and every 4 to 6 hours for DILAUDID Tablets. The dose of DILAUDID can be gradually adjusted until adequate pain relief and acceptable side effects have been achieved [see *Dosage and Administration (2.5)*].

#### Conversion from DILAUDID Oral Solution or DILAUDID Tablets to Extended-Release Hydromorphone Hydrochloride

The relative bioavailability of DILAUDID Oral Solution and DILAUDID Tablets compared to extended-release hydromorphone hydrochloride is unknown, so conversion to extended-release tablets must be accompanied by close observation for signs of excessive sedation and respiratory depression.

### **2.4 Dosage Modifications in Patients with Hepatic Impairment**

Initiate treatment with one-fourth to one-half the usual DILAUDID starting dose depending on the degree of impairment [see *Use in Specific Populations (8.6)*, and *Clinical Pharmacology (12.3)*].

### **2.5 Dosage Modifications in Patients with Renal Impairment**

Initiate treatment with one-fourth to one-half the usual DILAUDID starting dose depending on the degree of impairment [see *Use in Specific Populations (8.7)*, and *Clinical Pharmacology (12.3)*].

### **2.6 Titration and Maintenance of Therapy**

Individually titrate DILAUDID Oral Solution or DILAUDID Tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving DILAUDID Oral Solution or DILAUDID Tablets 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 (5.2)*]. 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 DILAUDID Oral Solution or DILAUDID Tablets 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.

For chronic pain, doses should be administered around-the-clock. A supplemental dose of 5 to 15% of the total daily usage may be administered every two hours on an as-needed basis.

### **2.7 Safe Reduction or Discontinuation of DILAUDID Oral Solution or DILAUDID**



## Tablets

Do not abruptly discontinue DILAUDID Oral Solution and DILAUDID Tablets in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

When a decision has been made to decrease the dose or discontinue therapy in an opioid dependent patient taking DILAUDID Oral Solution and DILAUDID Tablets, there are a variety of factors that should be considered, including the dose of DILAUDID Oral Solution and DILAUDID Tablets the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow-up plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with co-morbid pain and substance use disorders may benefit from referral to a specialist.

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on DILAUDID Oral Solution and DILAUDID Tablets who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include 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. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, monitor patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for a long duration and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic [see *Warnings and Precautions (5.13)*, *Drug Abuse and Dependence (9.3)*].

### 3 DOSAGE FORMS AND STRENGTHS

DILAUDID Oral Solution: 5 mg/5 mL (1 mg/mL) of hydromorphone hydrochloride in a clear, colorless to pale yellow, slightly viscous liquid.

DILAUDID Tablets:

- 2 mg tablets (light orange, round, flat-faced tablets, with beveled edges, debossed with a "P" on one side and the number "2" on the opposite side)
- 4 mg tablets (light yellow, round, flat-faced tablets, with beveled edges, debossed with a "P" on one side and the number "4" on the opposite side)
- 8 mg tablets (white, triangular shaped tablets, debossed with a "P" and an inverted "P" separated with a bisect on one side of the tablet and debossed with the number "8" on the other side of the tablet)

### 4 CONTRAINDICATIONS

DILAUDID Oral Solution and DILAUDID Tablets are contraindicated in patients with:

- Significant respiratory depression [see Warnings and Precautions (5.7)]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see Warnings and Precautions (5.7)]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see Warnings and Precautions (5.11)]
- Hypersensitivity to hydromorphone, hydromorphone salts, any other components of the product, or sulfite-containing medications (e.g., anaphylaxis) [see Warnings and Precautions (5.15), Adverse Reactions (6.1)]

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Risk of Accidental Overdose and Death due to Medication Errors

Dosing errors can result in accidental overdose and death. Ensure that the dose is communicated clearly and dispensed accurately. A household teaspoon or tablespoon is not an adequate measuring device. Given the inexactitude of the household spoon measure and the possibility of using a tablespoon instead of a teaspoon, which could lead to overdosage, the enclosed measuring device should be used or a calibrated measuring device obtained from the pharmacist. Healthcare providers should recommend a calibrated device that can measure and deliver the prescribed dose accurately, and instruct caregivers to use extreme caution in measuring the dosage.

#### 5.2 Addiction, Abuse, and Misuse

DILAUDID Oral Solution and DILAUDID Tablets contain hydromorphone, a Schedule II controlled substance. As an opioid, DILAUDID 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 DILAUDID Oral Solution or DILAUDID Tablets. 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 DILAUDID Oral Solution or DILAUDID Tablets, and monitor all patients receiving

DILAUDID Oral Solution or DILAUDID Tablets 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 DILAUDID Oral Solution or DILAUDID Tablets, but use in such patients necessitates intensive counseling about the risks and proper use of DILAUDID Oral Solution and DILAUDID Tablets along with intensive monitoring for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.4)*].

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing DILAUDID Oral Solution or DILAUDID Tablets. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [see *Patient Counseling Information (17)*]. 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.

### **5.3 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)**

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: [www.fda.gov/OpioidAnalgesicREMSPCG](http://www.fda.gov/OpioidAnalgesicREMSPCG).
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to [www.opioidanalgesicrems.com](http://www.opioidanalgesicrems.com). The FDA Blueprint can be found at [www.fda.gov/OpioidAnalgesicREMSBlueprint](http://www.fda.gov/OpioidAnalgesicREMSBlueprint).

### **5.4 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 (CO<sub>2</sub>) 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 DILAUDID Oral Solution or DILAUDID Tablets, 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 to 72 hours of initiating therapy with and following dosage increases of DILAUDID Oral Solution or DILAUDID Tablets.

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

Accidental ingestion of even one dose of DILAUDID Oral Solution or DILAUDID Tablets, especially by children, can result in respiratory depression and death due to an overdose of hydromorphone.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose [see *Patient Counseling Information (17)*].

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 (2.7)*].

#### Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with DILAUDID Oral Solution or DILAUDID Tablets. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered [see *Patient Counseling Information (17)*].

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone [see *Warnings and Precautions (5.2, 5.6)*, *Patient Counseling Information (17)*].

### **5.5 Neonatal Opioid Withdrawal Syndrome**

Prolonged use of DILAUDID Oral Solution or DILAUDID Tablets 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)*].

## **5.6 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 Oral Solution and DILAUDID Tablets 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.

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [*see Dosage and Administration (2.2), Warnings and Precautions (5.4)*].

Advise both patients and caregivers about the risks of respiratory depression and sedation when DILAUDID Oral Solution or DILAUDID Tablets are used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [*see Drug Interactions (7), Patient Counseling Information (17)*].

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

The use of DILAUDID Oral Solution or DILAUDID Tablets 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: DILAUDID Oral Solution- or DILAUDID Tablet-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 DILAUDID Oral Solution or DILAUDID Tablets [see *Warnings and Precautions (5.4)*].

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 (5.4)*].

Monitor such patients closely, particularly when initiating and titrating DILAUDID Oral Solution or DILAUDID Tablets and when DILAUDID is given concomitantly with other drugs that depress respiration [see *Warnings and Precautions (5.4)*]. Alternatively, consider the use of non-opioid analgesics in these patients.

## **5.8 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.

## **5.9 Severe Hypotension**

DILAUDID Oral Solution or DILAUDID Tablets 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 DILAUDID Oral Solution or DILAUDID Tablets. In patients with circulatory shock, DILAUDID may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of DILAUDID Oral Solution or DILAUDID Tablets in patients with circulatory shock.

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

In patients who may be susceptible to the intracranial effects of CO<sub>2</sub> retention (e.g., those with evidence of increased intracranial pressure or brain tumors), DILAUDID Oral Solution or DILAUDID Tablets may reduce respiratory drive, and the resultant CO<sub>2</sub> retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with DILAUDID

Oral Solution or DILAUDID Tablets.

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

### **5.11 Risks of Use in Patients with Gastrointestinal Conditions**

DILAUDID Oral Solution or DILAUDID Tablets are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The hydromorphone in DILAUDID Oral Solution or DILAUDID Tablets 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.

### **5.12 Increased Risk of Seizures in Patients with Seizure Disorders**

The hydromorphone in DILAUDID Oral Solution or DILAUDID Tablets 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 DILAUDID Oral Solution or DILAUDID Tablets therapy.

### **5.13 Withdrawal**

Do not abruptly discontinue DILAUDID Oral Solution or DILAUDID Tablets in a patient physically dependent on opioids. When discontinuing DILAUDID Oral Solution or DILAUDID Tablets in a physically dependent patient, gradually taper the dosage. Rapid tapering of hydromorphone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain [*see Dosage and Administration (2.7), Drug Abuse and Dependence (9.3)*].

Additionally, 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 DILAUDID Oral Solution or DILAUDID Tablets. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms [*see Drug Interactions (7)*].

### **5.14 Risks of Driving and Operating Machinery**

DILAUDID Oral Solution or DILAUDID Tablets 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 Oral Solution or DILAUDID Tablets and know how they will react to the medication.

### **5.15 Sulfites**

DILAUDID Oral Solution and DILAUDID Tablets contain 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. Use of DILAUDID Oral Solution and DILAUDID Tablets is contraindicated in patients with

hypersensitivity to sulfite-containing medications.

## **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 (5.2)*]
- Life-Threatening Respiratory Depression [see *Warnings and Precautions (5.4)*]
- Neonatal Opioid Withdrawal Syndrome [see *Warnings and Precautions (5.5)*]
- Interactions with Benzodiazepines or Other CNS Depressants [see *Warnings and Precautions (5.6)*]
- Adrenal Insufficiency [see *Warnings and Precautions (5.8)*]
- Severe Hypotension [see *Warnings and Precautions (5.9)*]
- Gastrointestinal Adverse Reactions [see *Warnings and Precautions (5.11)*]
- Seizures [see *Warnings and Precautions (5.12)*]
- Withdrawal [see *Warnings and Precautions (5.13)*]

### **6.1 Clinical Trial Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Serious adverse reactions associated with DILAUDID 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.

#### Less Frequently Observed Adverse Reactions

*Cardiac disorders:* tachycardia, bradycardia, palpitations

*Eye disorders:* vision blurred, diplopia, miosis, visual impairment

*Gastrointestinal disorders:* constipation, ileus, diarrhea, abdominal pain

*General disorders and administration site conditions:* weakness, feeling abnormal, chills

*Hepatobiliary disorders:* biliary colic

*Metabolism and nutrition disorders:* decreased appetite

*Musculoskeletal and connective tissue disorders:* muscle rigidity

*Nervous system disorders:* headache, tremor, paraesthesia, nystagmus, increased intracranial pressure, syncope, taste alteration, involuntary muscle contractions, presyncope

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

*Renal and urinary disorders:* urinary retention, urinary hesitation, antidiuretic effects



*Respiratory, thoracic, and mediastinal disorders:* bronchospasm, laryngospasm

*Skin and subcutaneous tissue disorders:* urticaria, rash, hyperhidrosis

*Vascular disorders:* flushing, hypotension, hypertension

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of hydromorphone. Because these reactions are 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.

Confusional state, convulsions, drowsiness, dyskinesia, dyspnea, erectile dysfunction, fatigue, hepatic enzymes increased, hyperalgesia, hypersensitivity reaction, lethargy, myoclonus, oropharyngeal swelling, peripheral edema, and somnolence.

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 DILAUDID Oral Solution or DILAUDID Tablets.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see *Clinical Pharmacology (12.2)*].

## 7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with DILAUDID.

**Table 1: Clinically Significant Drug Interactions with DILAUDID**

<b>Benzodiazepines and other Central Nervous System (CNS) Depressants</b>	
<i>Clinical Impact:</i>	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose [see <i>Dosage and Administration (2.2)</i> , <i>Warnings and Precautions (5.2, 5.4, 5.6)</i> ].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.

<b>Serotonergic Drugs</b>	
<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
<i>Intervention:</i>	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue DILAUDID Oral Solution or DILAUDID Tablets if serotonin syndrome is suspected.
<i>Examples:</i>	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT <sub>3</sub> receptor antagonists, drugs that affect 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).
<b>Monoamine Oxidase Inhibitors (MAOIs)</b>	
<i>Clinical Impact:</i>	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see <i>Warnings and Precautions (5.4)</i> ]. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.
<i>Intervention:</i>	The use of DILAUDID Oral Solution or DILAUDID Tablets is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
<i>Examples:</i>	Phenelzine, tranylcypromine, and linezolid.
<b>Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics</b>	
<i>Clinical Impact:</i>	May reduce the analgesic effect of DILAUDID Oral Solution or DILAUDID Tablets and/or precipitate withdrawal symptoms.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	Butorphanol, nalbuphine, pentazocine, and buprenorphine.
<b>Muscle Relaxants</b>	
<i>Clinical Impact:</i>	Hydromorphone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of DILAUDID Oral Solution or DILAUDID Tablets and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose [see <i>Dosage and Administration (2.2)</i> , <i>Warnings and Precautions (5.4, 5.6)</i> ].
<b>Diuretics</b>	
<i>Clinical Impact:</i>	Opioids can reduce the efficacy of diuretics by inducing the

<i>Impact:</i>	release of antidiuretic hormone.
<i>Intervention:</i>	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
<b>Anticholinergic Drugs</b>	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
<i>Intervention:</i>	Monitor patients for signs of urinary retention or reduced gastric motility when DILAUDID Oral Solution or DILAUDID Tablets is used concomitantly with anticholinergic drugs.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see *Warnings and Precautions (5.5)*]. There are no available data with DILAUDID in pregnant women to inform a drug-associated risk for major birth defects and miscarriage.

In animal reproduction studies, reduced postnatal survival of pups, and decreased were noted following oral treatment of pregnant rats with hydromorphone during gestation and through lactation at doses 0.8 times the human daily dose of 24 mg/day (HDD), respectively. In published studies, neural tube defects were noted following subcutaneous injection of hydromorphone to pregnant hamsters at doses 6.4 times the HDD and soft tissue and skeletal abnormalities were noted following subcutaneous continuous infusion of 3 times the HDD to pregnant mice. No malformations were noted at 4 or 40.5 times the HDD in pregnant rats or rabbits, respectively [see *Data*]. Based on animal data, advise pregnant women of the potential risk to a fetus.

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 [see *Warnings and Precautions (5.5)*].

### *Labor or Delivery*

Opioids cross the placenta and may produce respiratory depression and psychophysiological effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. DILAUDID Oral Solution or DILAUDID Tablets is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including DILAUDID Oral Solution or DILAUDID Tablets, 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*

Pregnant rats were treated with hydromorphone hydrochloride from Gestation Day 6 to 17 via oral gavage doses of 1, 5, or 10 mg/kg/day (0.4, 2, or 4 times the HDD of 24 mg based on body surface area, respectively). Maternal toxicity was noted in all treatment groups (reduced food consumption and body weights in the two highest dose groups). There was no evidence of malformations or embryotoxicity reported.

Pregnant rabbits were treated with hydromorphone hydrochloride from Gestation Day 7 to 19 via oral gavage doses of 10, 25, or 50 mg/kg/day (8.1, 20.3, or 40.5 times the HDD of 24 mg based on body surface area, respectively). Maternal toxicity was noted in the two highest dose groups (reduced food consumption and body weights). There was no evidence of malformations or embryotoxicity reported.

In a published study, neural tube defects (exencephaly and cranioschisis) were noted following subcutaneous administration of hydromorphone hydrochloride (19 to 258 mg/kg) on Gestation Day 8 to pregnant hamsters (6.4 to 87.2 times the HDD of 24 mg/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/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 sternbrae, delayed ossification of the paws and ectopic ossification sites) were observed at doses 3 times the human dose of 24 mg/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 Oral Solution or DILAUDID Tablets and any potential adverse effects on the breastfed infant from DILAUDID Oral Solution or DILAUDID Tablets or from the underlying maternal condition.

### Clinical Considerations

Monitor infants exposed to DILAUDID 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 (6.2), Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)*].

## **8.4 Pediatric Use**

The safety and effectiveness of DILAUDID in pediatric patients have 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 slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [*see Warnings and Precautions (5.7)*].

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 is affected by hepatic impairment. Due to increased exposure of hydromorphone, patients with 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 is affected by renal impairment. In addition, in patients with severe renal impairment, hydromorphone appeared to be more slowly eliminated with a longer terminal elimination half-life. 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 Oral Solution and DILAUDID Tablets contain hydromorphone, a Schedule II controlled substance.

### **9.2 Abuse**

DILAUDID Oral Solution and DILAUDID Tablets contain hydromorphone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, oxycodone, methadone, morphine, oxymorphone and tapentadol. DILAUDID Oral Solution and DILAUDID Tablets can be abused and is subject to misuse, addiction, and criminal diversion [see *Warnings and Precautions (5.2)*].

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 with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common

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

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

### Risks Specific to Abuse of DILAUDID

DILAUDID Oral Solution and DILAUDID Tablets are for oral use only. Abuse of DILAUDID Oral Solution or DILAUDID Tablets poses a risk of overdose and death. The risk is increased with concurrent abuse of DILAUDID ORAL LQIUID or DILAUDID Tablets 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 is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting in withdrawal symptoms after abrupt discontinuation or 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.

Do not abruptly discontinue DILAUDID Oral Solution and DILAUDID Tablets in a patient physically dependent on opioids. Rapid tapering of DILAUDID Oral Solution and DILAUDID Tablets in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing DILAUDID Oral Solution and DILAUDID Tablets, gradually taper the dosage using a patient-specific plan that considers the following: the dose of DILAUDID Oral Solution and DILAUDID Tablets the patient has been taking, the duration of

treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for a long duration at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper [see *Dosage and Administration (2.7)*, *Warnings and Precautions (5.13)*].

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 Oral Solution or DILAUDID Tablets 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 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.

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

Because the duration of opioid reversal is expected to be less than the duration of action of hydromorphone in DILAUDID Oral Solution or DILAUDID Tablets, 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**

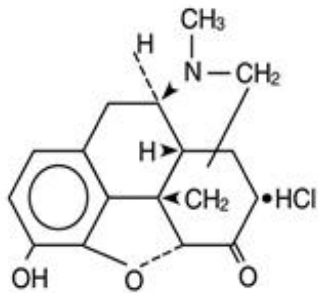
DILAUDID (hydromorphone hydrochloride), a hydrogenated ketone of morphine, is an opioid agonist.



DILAUDID Tablets are supplied in 2 mg, 4 mg, and 8 mg tablets for oral administration. The tablet strengths describe the amount of hydromorphone hydrochloride in each tablet.

DILAUDID Oral Solution is supplied as 5mg/5 mL (1 mg/mL) viscous liquid.

The chemical name is 4,5 $\alpha$ -epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride. The molecular Weight is 321.80. Its molecular formula is C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub>•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 2 mg, 4 mg, and 8 mg tablets contain the following inactive ingredients: lactose anhydrous and magnesium stearate. DILAUDID Tablets may also contain traces of sodium metabisulfite.

The 2 mg tablets also contain D&C red #30 Lake dye and D&C yellow #10 Lake dye.

The 4 mg tablets also contain D&C yellow #10 Lake dye.

Each 5 mL (1 teaspoon) of DILAUDID Oral Solution contains 5 mg of hydromorphone hydrochloride. The inactive ingredients are purified water, methylparaben, propylparaben, sucrose, and glycerin. DILAUDID Oral Solution may contain traces of sodium metabisulfite.

## 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 action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and to 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 origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

## Effects on the Gastrointestinal Tract and Other Smooth Muscle

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 (6.2)*]. 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 (6.2)*].

## 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, 2.6)].

### 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 (2.3, 2.4, 2.6)].

## **12.3 Pharmacokinetics**

### Absorption

The analgesic activity of DILAUDID (hydromorphone hydrochloride) is due to the parent drug, hydromorphone. Hydromorphone is rapidly absorbed from the gastrointestinal tract after oral administration and undergoes extensive first-pass metabolism. Exposure of hydromorphone ( $C_{max}$  and  $AUC_{0-24}$ ) is dose-proportional at a dose range of 2 and 8 mg. *In vivo* bioavailability following single-dose administration of the 8 mg tablet is approximately 24% (coefficient of variation 21%). Bioequivalence between the DILAUDID 8 mg TABLET and an equivalent dose of DILAUDID Oral Solution has been demonstrated.

After oral administration of DILAUDID, peak plasma hydromorphone concentrations are generally attained within ½ to 1 hour.

<b>Mean (%cv)</b>				
<b>Dosage Form</b>	<b><math>C_{max}</math> (ng)</b>	<b><math>T_{max}</math> (hrs)</b>	<b>AUC (ng*hr/mL)</b>	<b><math>T_{1/2}</math> (hrs)</b>
8 mg Tablet	5.5 (33%)	0.74 (34%)	23.7 (28%)	2.6 (18%)
8 mg Oral Liquid	5.7 (31%)	0.73 (71%)	24.6 (29%)	2.8 (20%)

### Food Effects

In a study conducted with a single 8 mg dose of hydromorphone (2 mg hydromorphone immediate-release tablets), food lowered  $C_{max}$  by 25%, prolonged  $T_{max}$  by 0.8 hour, and increased AUC by 35%. The effects may not be clinically relevant.

### Distribution

At therapeutic plasma levels, hydromorphone is approximately 8 to 19% bound to plasma proteins. After an intravenous bolus dose, the steady state of volume 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.

### Specific Populations

#### *Hepatic Impairment*

After oral administration of a single 4 mg dose (2 mg hydromorphone immediate-release tablets), mean exposure to hydromorphone ( $C_{max}$  and  $AUC_{\infty}$ ) is increased 4-fold in patients with moderate (Child-Pugh Group B) hepatic impairment compared with subjects with normal hepatic function. Due to increased exposure of hydromorphone, patients with moderate hepatic impairment should be started at a lower dose and closely monitored during dose titration. Pharmacokinetics of hydromorphone in severe hepatic impairment patients has not been studied. Further increase in  $C_{max}$  and  $AUC$  of hydromorphone in this group is expected. As such, starting dose should be even more conservative [see *Use in Specific Populations (8.6)*].

#### *Renal Impairment*

After oral administration of a single 4 mg dose (2 mg hydromorphone immediate-release tablets), exposure to hydromorphone ( $C_{max}$  and  $AUC_{0-48}$ ) is increased in patients with impaired renal function by 2-fold in moderate ( $CL_{cr} = 40$  to  $60$  mL/min) and 3-fold in 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 longer terminal elimination half-life (40 hr) compared to patients with normal renal function (15 hr). Patients with moderate renal impairment should be started on a lower dose. Starting doses for patients with severe renal impairment should be even lower. Patients with renal impairment should be closely monitored during dose titration [see *Use in Specific Populations (8.7)*].

#### *Age: 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 higher  $C_{max}$  (25%) than males with comparable  $AUC_{0-24}$  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.

## **14 CLINICAL STUDIES**

Analgesic effects of single doses of DILAUDID Oral Solution administered to patients with post-surgical pain have been studied in double-blind controlled trials. In one study, both 5 mg and 10 mg of DILAUDID Oral Solution provided significantly more analgesia than placebo. In another trial, 5 mg and 10 mg of DILAUDID Oral Solution were compared to 30 mg and 60 mg of morphine sulfate oral liquid. The pain relief provided by 5 mg and 10 mg DILAUDID Oral Solution was comparable to 30 mg and 60 mg oral morphine sulfate, respectively.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

DILAUDID is available as follows:

**Oral Solution 5 mg/5 mL:** a clear, colorless to pale yellow, slightly viscous liquid.

**NDC 42858-416-16: Bottles of 1 pint (473 mL)**

**2 mg Tablets:** light orange, round, flat-faced tablets, with beveled edges, debossed with a "P" on one side and the number "2" on the opposite side.

**NDC 42858-122-01: Bottles of 100**

**4 mg Tablets:** light yellow, round, flat-faced tablets, with beveled edges, debossed with a "P" on one side and the number "4" on the opposite side.

**NDC 42858-234-01: Bottles of 100**

**NDC 42858-234-50: Bottles of 500**

**8 mg Tablets:** white, triangular shaped tablets debossed with a "P" and an inverted "P" separated with a bisect on one side of the tablet and debossed with the number "8" on the other side of the tablet.

**NDC 42858-338-01: Bottles of 100**

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

Protect from light.

Store DILAUDID Oral Solution and DILAUDID Tablets securely and dispose of properly [see *Patient Counseling Information (17)*].

## **17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

### Storage and Disposal

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store DILAUDID Oral Solution and DILAUDID Tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home [see *Warnings and Precautions (5.2, 5.4), Drug Abuse and Dependence (9.2)*]. Inform patients that leaving DILAUDID Oral Solution and DILAUDID Tablets unsecured can pose a deadly risk to others in the home.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Expired, unwanted, or unused DILAUDID Oral Solution and DILAUDID Tablets should be disposed of by flushing the unused medication down the toilet if a drug take-back option is not readily available. Inform patients that they can visit [www.fda.gov/drugdisposal](http://www.fda.gov/drugdisposal) for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines.

### Medication Errors

Instruct patients how to measure and take the correct dose of DILAUDID, and to always use the enclosed cup when administering DILAUDID Oral Solution to ensure the dose is measured and administered accurately [see *Warnings and Precautions (5.1)*].

If the prescribed concentration is changed, instruct patients on how to correctly measure the new dose to avoid errors which could result in accidental overdose and death.

### Addiction, Abuse, and Misuse

Inform patients that the use of DILAUDID Oral Solution or DILAUDID Tablets, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see *Warnings and Precautions (5.2)*]. Instruct patients not to share DILAUDID Oral Solution or DILAUDID Tablets with others and to take steps to protect DILAUDID Oral Solution or DILAUDID Tablets from theft or misuse.

### Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting DILAUDID Oral Solution or DILAUDID Tablets or when the dosage is increased, and that it can occur even at recommended dosages.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose [see *Warnings and Precautions (5.4)*].

## Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, both when initiating and renewing treatment with DILAUDID Oral Solution or DILAUDID Tablets. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.4)*]).

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that naloxone's effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered [see *Overdosage (10)*].

If naloxone is prescribed, also advise patients and caregivers:

- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone and to keep it in a place where family and friends can access it in an emergency
- To read the Patient Information (or other educational material) that will come with their naloxone. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

## Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [see *Warnings and Precautions (5.4)*].

## Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if DILAUDID Oral Solution or DILAUDID Tablets are used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider [see *Warnings and Precautions (5.5)*, *Drug Interactions (7)*].

## Serotonin Syndrome

Inform patients that DILAUDID 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)*].

## MAOI Interaction

Inform patients to avoid taking DILAUDID Oral Solution or DILAUDID Tablets while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking DILAUDID Oral Solution or DILAUDID Tablets [see *Drug Interactions (7)*].

## Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms

and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [see *Warnings and Precautions (5.8)*].

### Important Administration Instructions

Instruct patients how to properly take DILAUDID.

- Advise patients to always obtain a calibrated oral syringe/dosing cup from the pharmacist for administering DILAUDID Oral Solution to ensure that the dose is measured and administered accurately [see *Warnings and Precautions (5.1)*]. Advise patients never to use household teaspoons or tablespoons to measure DILAUDID Oral Solution.
- Advise patients not to adjust the dose of DILAUDID Oral Solution or DILAUDID Tablets without consulting with a physician or other healthcare professional.

### Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue DILAUDID Oral Solution or DILAUDID Tablets without first discussing a tapering plan with the prescriber [see *Dosage and Administration (2.7)*].

### Hypotension

Inform patients that DILAUDID Oral Solution or DILAUDID Tablets may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) [see *Warnings and Precautions (5.9)*].

### Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in DILAUDID Oral Solution or DILAUDID Tablets. Advise patients how to recognize such a reaction and when to seek medical attention [see *Contraindications (4)*, *Adverse Reactions (6)*].

### Pregnancy

#### *Neonatal Opioid Withdrawal Syndrome*

Inform female patients of reproductive potential that prolonged use of DILAUDID Oral Solution or DILAUDID Tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [see *Warnings and Precautions (5.5)*, *Use in Specific Populations (8.1)*].

#### *Embryo-Fetal Toxicity*

Inform female patients of reproductive potential that DILAUDID Oral Solution or DILAUDID Tablets can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy [see *Use in Specific Populations (8.1)*, *Warnings and Precautions (5.5)*]

### Lactation

Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs [see *Use in Specific Populations (8.2)*].



## Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [see *Use in Specific Population (8.3)*].

## Driving or Operating Heavy Machinery

Inform patients that DILAUDID Oral Solution or DILAUDID Tablets may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [see *Warnings and Precautions (5.14)*].

## Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [see *Adverse Reactions (6)*, *Clinical Pharmacology (12.2)*].

Healthcare professionals can telephone Rhodes Pharmaceuticals L.P.'s Medical Services Department (1-888-827-0616) for information on this product.

### **Manufactured by:**

Halo Pharmaceutical, Inc.  
Whippany, NJ 07981

### **Marketed by:**

Rhodes Pharmaceuticals L.P.  
Coventry, RI 02816

304374-0F

Revised: 05/2022

## **Medication Guide**

### **DILAUDID® (dī-law-did)**

### **(hydromorphone hydrochloride) Tablets and Oral Solution, CII**

#### **DILAUDID Tablets and DILAUDID Oral Solution are:**

- Strong prescription pain medicines that contains an opioid (narcotic) that is used to manage pain severe enough to require an opioid analgesic, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- Opioid pain medicines that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

#### **Important information about DILAUDID:**

- **Get emergency help or call 911 right away if you take too much DILAUDID Tablets or DILAUDID Oral Solution (overdose).** When you first start taking **DILAUDID Tablets or DILAUDID Oral Solution**, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Taking **DILAUDID Tablets or DILAUDID Oral Solution** with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants

(including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.

- Never give anyone else your DILAUDID Tablets or DILAUDID Oral Solution. They could die from taking it. Selling or giving away DILAUDID Tablets or DILAUDID Oral Solution is against the law.
- Store DILAUDID Tablets or DILAUDID Oral Solution securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

**Do not take DILAUDID Tablets or DILAUDID Oral Solution if you have:**

- Severe asthma, trouble breathing, or other lung problems.
- A bowel blockage or have narrowing of the stomach or intestines.

**Before taking DILAUDID Tablets or DILAUDID Oral Solution, tell your healthcare provider if you have a history of:**

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems

**Tell your healthcare provider if you are:**

- **Pregnant or planning to become pregnant.** Prolonged use of DILAUDID Tablets and DILAUDID Oral Solution during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **Breastfeeding.** DILAUDID Tablets or DILAUDID Oral Solution pass into breast milk and may harm your baby.
- Living in a household where there are small children or someone who has abused street or a prescription drugs.
- Taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking DILAUDID with certain other medicines can cause serious side effects that could lead to death.

**When taking DILAUDID:**

- Do not change your dose. Take DILAUDID exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking DILAUDID Tablets or DILAUDID Oral Solution regularly, do not stop taking DILAUDID Tablets or DILAUDID Oral Solution without talking to your healthcare provider.
- Dispose of expired, unwanted, or unused DILAUDID Tablets or DILAUDID Oral Solution by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit [www.fda.gov/drugdisposal](http://www.fda.gov/drugdisposal) for additional information on disposal of unused medicines.

**While taking DILAUDID DO NOT:**

- Drive or operate heavy machinery, until you know how DILAUDID Tablets or DILAUDID Oral Solution affects you. DILAUDID can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with DILAUDID Tablets or DILAUDID Oral Solution may cause you to overdose and die.

**The possible side effects of DILAUDID Tablets and DILAUDID Oral Solution:**

- Constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

**Get emergency medical help or call 911 right away if you have:**

- Trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of DILAUDID Tablets and DILAUDID Oral Solution. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information, go to**

**[dailymed.nlm.nih.gov](http://dailymed.nlm.nih.gov)**

Marketed by: Rhodes Pharmaceuticals L.P., Coventry, RI 02816 US,  
<http://rhodespharma.com> or call 1-888-827-0616

**This Medication Guide has been approved by  
the U.S. Food and Drug Administration.**

Issued:  
03/2021

**PRINCIPAL DISPLAY PANEL - 2 mg Tablet Bottle Label**

**NDC 42858-122-01**

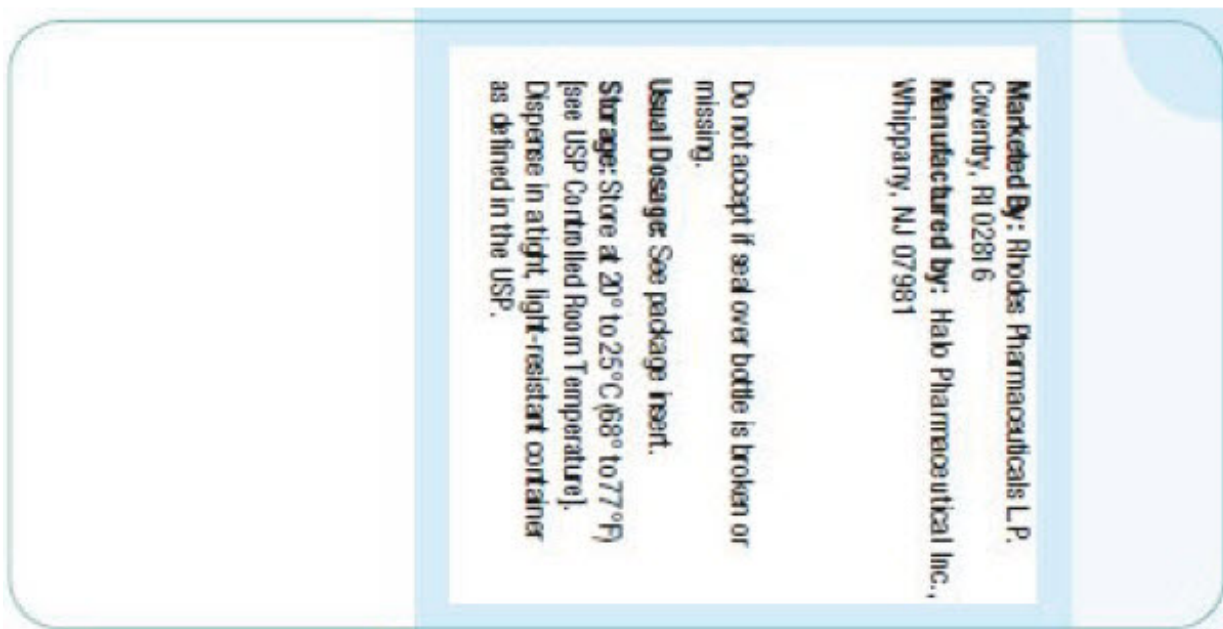
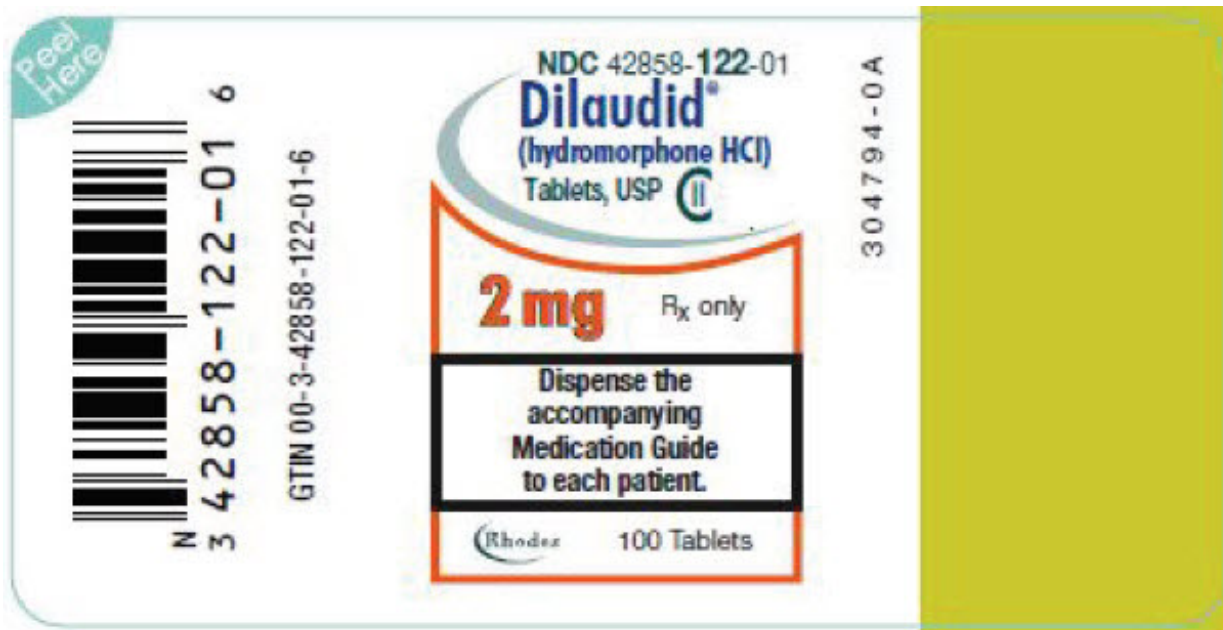
**Dilaudid®  
(hydromorphone HCl)  
Tablets, USP  
CII**

**2 mg**  
Rx only

**Dispense the  
accompanying  
Medication Guide  
to each patient.**

Rhodes

100 Tablets



**PRINCIPAL DISPLAY PANEL - 4 mg Tablet Bottle Label**

**NDC 42858-234-01**

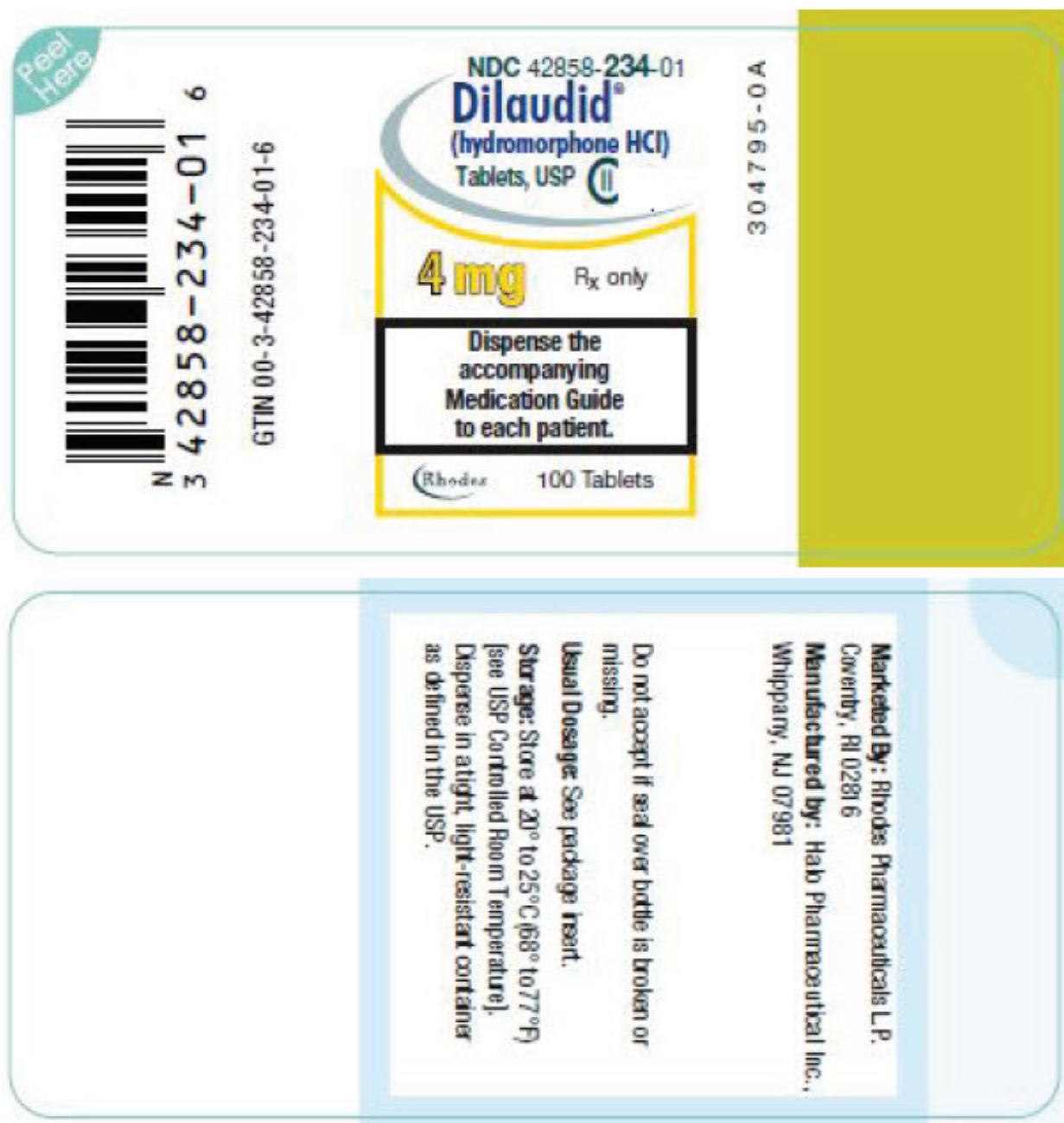
**Dilaudid®  
(hydromorphone HCl)  
Tablets, USP  
CII**

**4 mg  
Rx only**

**Dispense the  
accompanying  
Medication Guide  
to each patient.**

Rhodes

100 Tablets



**PRINCIPAL DISPLAY PANEL - 8 mg Tablet Bottle Label**

**NDC 42858-338-01**

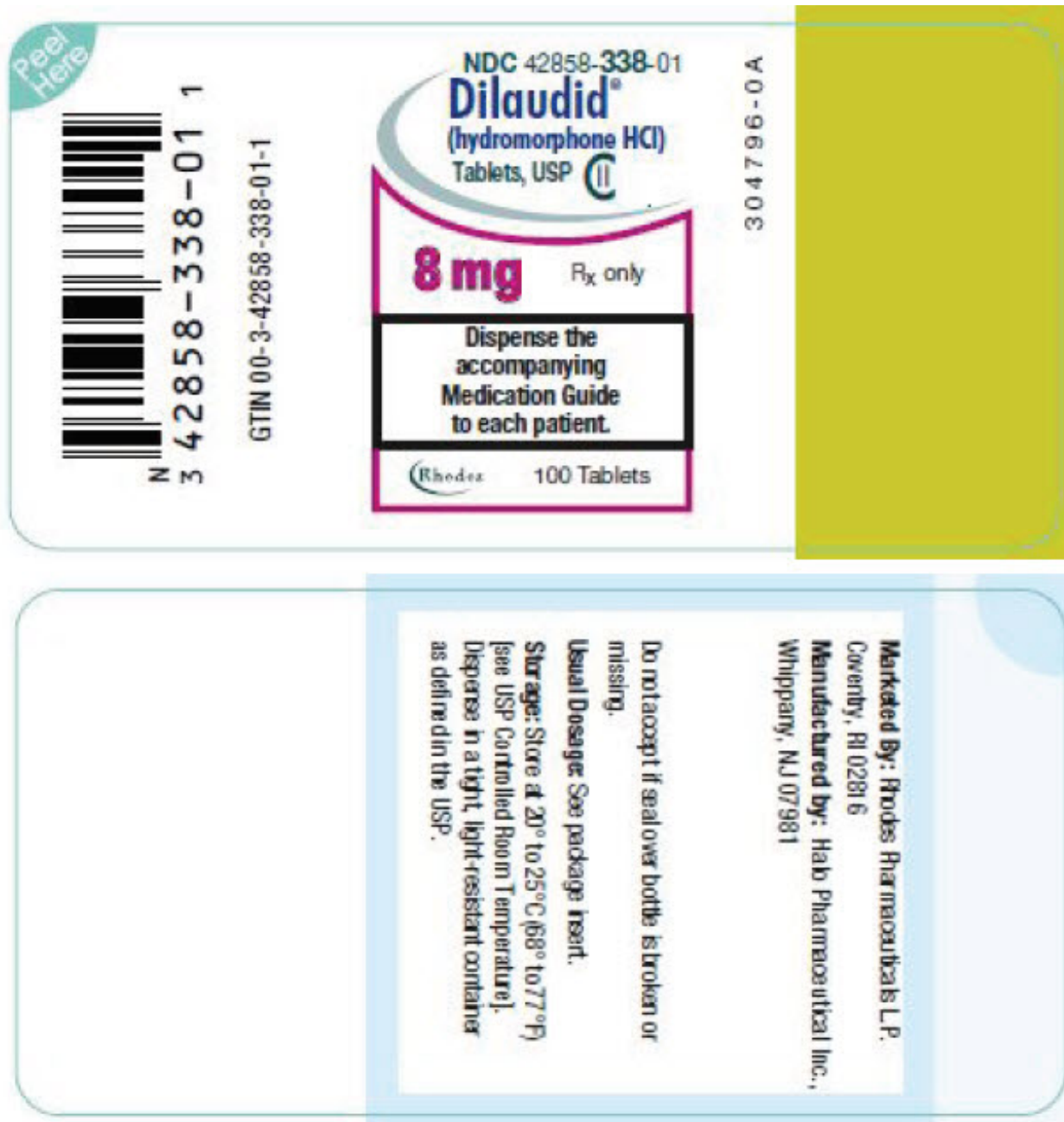
**Dilaudid®  
(hydromorphone HCl)  
Tablets, USP  
CII**

**8 mg  
Rx only**

**Dispense the accompanying Medication Guide to each patient.**

Rhodes

100 Tablets



**PRINCIPAL DISPLAY PANEL - 473 mL Bottle Label**

**NDC 42858-416-16**

**Dilaudid®  
(hydromorphone HCl)  
Oral Solution, USP**

CII

5 mg/5 mL  
(1 mg/mL)

One Pint (473 mL)


**Dispense the accompanying  
Medication Guide to each patient.**

Rhodes

R<sub>x</sub> Only

304371-0A

NDC 42858-416-16

**Dilaudid<sup>®</sup>**  
(hydromorphone HCl)  
Oral Solution, USP 

**5 mg/5 mL**  
**(1 mg/mL)**

One Pint (473 mL)

**Dispense the accompanying  
Medication Guide to each patient.**

Rhodes R<sub>x</sub> Only


304371-0A

Each 5 mL (1 teaspoonful) contains:  
Hydromorphone Hydrochloride...5 mg  
Do not accept if band on cap is broken  
or missing.

**Usual Dose:** See package insert.

**Storage:** Store at 25°C (77°F);  
excursions permitted to 15° to 30°C  
(59° to 86°F) [see USP Controlled  
Room Temperature]. Shake well  
before using. Dispense in a tight,  
light-resistant Container as defined  
in the USP.

Marketed by:  
Rhodes Pharmaceuticals L.P.  
Coventry, RI 02816

  
N 42858-416-16 0

## DILAUDID

hydromorphone hydrochloride tablet

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:42858-122
<b>Route of Administration</b>	ORAL	<b>DEA Schedule</b>	CII

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
hydromorphone hydrochloride (UNII: L960UP2KRW) (hydromorphone -	hydromorphone	2 mg

UNII:Q812464R06)	hydrochloride	2 mg		
<b>Inactive Ingredients</b>				
<b>Ingredient Name</b>		<b>Strength</b>		
D&C Red No. 30 (UNII: 2S42T2808B)				
D&C Yellow No. 10 (UNII: 35SW5USQ3G)				
Anhydrous Lactose (UNII: 3SY5LH9PMK)				
Magnesium Stearate (UNII: 70097M6I30)				
Sodium metabisulfite (UNII: 4VON5FNS3C)				
<b>Product Characteristics</b>				
<b>Color</b>	ORANGE (light orange)	<b>Score</b>	2 pieces	
<b>Shape</b>	ROUND (flat-faced with beveled edges)	<b>Size</b>	5mm	
<b>Flavor</b>		<b>Imprint Code</b>	P;2	
<b>Contains</b>				
<b>Packaging</b>				
<b>#</b>	<b>Item Code</b>	<b>Package Description</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
1	NDC:42858-122-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	05/15/2017	
<b>Marketing Information</b>				
<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>	
NDA	NDA019892	05/15/2017		

<b>DILAUDID</b>			
hydromorphone hydrochloride tablet			
<b>Product Information</b>			
<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:42858-234
<b>Route of Administration</b>	ORAL	<b>DEA Schedule</b>	CII
<b>Active Ingredient/Active Moiety</b>			
<b>Ingredient Name</b>		<b>Basis of Strength</b>	<b>Strength</b>
hydromorphone hydrochloride (UNII: L960UP2KRW) (hydromorphone - UNII:Q812464R06)		hydromorphone hydrochloride	4 mg
<b>Inactive Ingredients</b>			



Ingredient Name	Strength
<b>D&amp;C Yellow No. 10</b> (UNII: 35SW5USQ3G)	
<b>Anhydrous Lactose</b> (UNII: 3SY5LH9PMK)	
<b>Magnesium Stearate</b> (UNII: 70097M6I30)	
<b>Sodium metabisulfite</b> (UNII: 4VON5FNS3C)	

### Product Characteristics

<b>Color</b>	YELLOW (light yellow)	<b>Score</b>	2 pieces
<b>Shape</b>	ROUND (flat-faced with beveled edges)	<b>Size</b>	6mm
<b>Flavor</b>		<b>Imprint Code</b>	P;4
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42858-234-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	05/15/2017	
2	NDC:42858-234-50	500 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	05/15/2017	

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA019892	05/15/2017	

## DILAUDID

hydromorphone hydrochloride tablet

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:42858-338
<b>Route of Administration</b>	ORAL	<b>DEA Schedule</b>	CII

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>hydromorphone hydrochloride</b> (UNII: L960UP2KRW) (hydromorphone - UNII:Q812464R06)	hydromorphone hydrochloride	8 mg

### Inactive Ingredients

Ingredient Name	Strength
<b>Anhydrous Lactose</b> (UNII: 3SY5LH9PMK)	
<b>Magnesium Stearate</b> (UNII: 70097M6I30)	
<b>Sodium metabisulfite</b> (UNII: 4VON5FNS3C)	

## Product Characteristics

<b>Color</b>	WHITE	<b>Score</b>	2 pieces
<b>Shape</b>	TRIANGLE (triangular shaped)	<b>Size</b>	7mm
<b>Flavor</b>		<b>Imprint Code</b>	Pd;8
<b>Contains</b>			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42858-338-01	100 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	05/15/2017	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA019892	05/15/2017	

## DILAUDID

hydromorphone hydrochloride solution

## Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:42858-416
<b>Route of Administration</b>	ORAL	<b>DEA Schedule</b>	CII

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>hydromorphone hydrochloride</b> (UNII: L960UP2KRW) (hydromorphone - UNII:Q812464R06)	hydromorphone hydrochloride	5 mg in 5 mL

## Inactive Ingredients

Ingredient Name	Strength
<b>Water</b> (UNII: 059QF0KO0R)	
<b>Methylparaben</b> (UNII: A218C7HI9T)	
<b>Propylparaben</b> (UNII: Z8IX2SC1OH)	
<b>Sucrose</b> (UNII: C151H8M554)	
<b>Glycerin</b> (UNII: PDC6A3C0OX)	
<b>Sodium metabisulfite</b> (UNII: 4VON5FNS3C)	

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42858-416-16	473 mL in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	05/15/2017	
<b>Marketing Information</b>				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA019891	05/15/2017		

**Labeler** - Rhodes Pharmaceuticals L.P. (831928986)

Revised: 5/2022

Rhodes Pharmaceuticals L.P.