PRESCRIBING INFORMATION

INCLUDING PATIENT MEDICATION INFORMATION

[N]DILAUDID®

HYDROmorphone* hydrochloride

Tablets, 1 mg, 2 mg, 4 mg and 8 mg, Oral
Sterile Solution for Injection, 2 mg/mL, Intramuscular, Intravenous, Subcutaneous

USP Standard

Opioid Analgesic

NOT A PRODUCT MONOGRAPH

Purdue Pharma
3381 Steeles Avenue East Suite 310
Toronto, ON
M2H 3S7

Date of Initial Approval:
August 8, 2008

Date of Revision:
July 7, 2021

Submission Control No: 237679

*HYDROmorphone is the name of the active chemical ingredient (hydromorphone) and is not a brandname/tradename.

RECENT MAJOR LABEL CHANGES

3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Life-Threatening Respiratory Depression, Mar 2018
4 DOSING AND ADMINISTRATION, 4.2 Recommended Dose and Dose Adjustment, Patients Currently Receiving Opioids, Mar 2018
4 DOSING AND ADMINISTRATION, 4.3 Administration, Mar 2018
7 WARNINGS AND PRECAUTIONS, Use in Drug and Alcohol Addiction, Mar 2018
7 WARNINGS AND PRECAUTIONS, Neurologic, Serotonin toxicity / Serotonin syndrome July 2020
7 WARNINGS AND PRECAUTIONS, Respiratory, Sleep Apnea, July 2020
7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women, Mar 2018
7 WARNINGS AND PRECAUTIONS, 7.1.2 Breast-feeding, Mar 2018

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DILAUDID® (HYDROmorphone hydrochloride) is indicated for the relief of moderate to severe pain in adults.

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of DILAUDID has not been studied in the pediatric population. Therefore the use of DILAUDID is not recommended in patients under 18 years of age.

1.2 Geriatrics

Geriatrics (>65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, and titrated slowly, reflecting the greater frequency of decreased hepatic, renal or cardiac function, concomitant disease or other drug therapy (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

2 CONTRAINDICATIONS

DILAUDID (HYDROmorphone hydrochloride) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients who are hypersensitive to other opioid analgesics.
- Patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide (CO_2) levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, pregnant, or during labour and delivery (see SERIOUS WARNINGS AND PRECAUTIONS BOX and WARNINGS AND PRECAUTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with immediate release opioid formulations, DILAUDID (HYDROmorphone hydrochloride) should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse
DILAUDID poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing DILAUDID, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). DILAUDID should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression: OVERDOSE
Serious, life-threatening, or fatal respiratory depression may occur with use of DILAUDID. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of DILAUDID or following a dose increase.

DILAUDID tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving DILAUDID can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS). Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure
Accidental ingestion of even one dose of DILAUDID, especially by children, can result in a fatal overdose of HYDROmorphone (see STORAGE, STABILITY AND DISPOSAL for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of DILAUDID during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

Interaction with Alcohol
The co-ingestion of alcohol with DILAUDID should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Risks From Concomitant Use with Benzodiazepines or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- Reserve concomitant prescribing of DILAUDID and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.

- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

For acute pain, it is recommended that DILAUDID be used for a maximum of 7 days at the lowest dose that provides adequate pain relief.

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. For the management of chronic non-cancer, non-palliative pain, it is recommended that 18 mg (90 morphine milligram equivalent) daily of DILAUDID not be exceeded. Each patient should be assessed for their risk prior to prescribing DILAUDID, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of DILAUDID (see DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

DILAUDID should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, or not tolerated, or would be otherwise inadequate to provide appropriate management of pain.

DILAUDID tablets must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving DILAUDID tablets can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS).

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression.

DILAUDID tablets should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see WARNINGS AND PRECAUTIONS, Peri-operative Considerations).

DILAUDID is not indicated for rectal administration.

Sterile Solution for Injection: DILAUDID sterile solution for injection is to be visually inspected prior to use. Only clear solutions practically free from particles should be used. The injection should be given immediately after opening the ampoule. Once opened, any unused portion should be discarded.

4.2 Recommended Dose and Dosage Adjustment

Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric use (see INDICATIONS).

Adults (≥18 years of age): Individual dosing requirements vary considerably based on each patient's age, weight, severity and cause of pain, and medical and analgesic history.

Patients Not Receiving Opioids at the Time of Initiation of DILAUDID Treatment
Oral: Orally for adults, 2 to 4 mg every 4 to 6 hours as required.

Parenteral: The usual adult parenteral dose for pain relief is 2 mg by subcutaneous or intramuscular route every 4 to 6 hours as necessary. If necessary, DILAUDID may be given intravenously, but the injection should be given very slowly. Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression. Severe pain can be controlled with 3 to 4 mg every 4 to 6 hours as necessary.

DILAUDID injection has been reported to be physically or chemically incompatible with solutions containing sodium bicarbonate and thiopenthal sodium.

Patients Currently Receiving Opioids
For patients who are receiving an alternate opioid, the "oral HYDROmorphone equivalent" of the analgesic presently being used, should be determined. Having determined the total daily dosage of the present analgesic, Table 1 can be used to calculate the approximate daily oral HYDROmorphone dosage that should provide equivalent analgesia. Further dose reductions should be considered due to incomplete cross-tolerance between opioids.

Opioid Rotation: Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other factors. When switching from one opioid to another, **consider reducing the calculated dose by 25-50%** to minimize the risk of overdose. Subsequently, up-titrate the dose, as required, to reach the appropriate maintenance dose.

Table 1 – Opioid Conversion Table[a]

Opioids	To convert to oral morphine equivalent	To convert from oral morphine multiply by	Daily 90 mg MED[b]
Morphine	1	1	90 mg
Codeine	0.15	6.67	600 mg
Hydromorphone	5	0.2	18 mg
Oxycodone	1.5	0.667	60 mg
Tapentadol	0.3-0.4	2.5-3.33	300 mg
Tramadol	0.1-0.2	6	***
Methadone	Morphine dose equivalence is not reliably established		

*** The maximum recommended daily dose of tramadol is 300 mg – 400 mg depending on the formulation.
a. Adapted from the 2017 Canadian guideline for opioids for chronic non-cancer pain. McMaster University; 2017
b. MED. Morphine Equivalent Dose

Patients with Hepatic Impairment
Start patients on one-fourth to one-half the usual DILAUDID injection starting dose depending on the degree of impairment. Closely monitor patients with moderate hepatic impairment for respiratory and central nervous system depression during initiation of therapy with DILAUDID and during dose titration. Use of alternate analgesics is recommended for patients with severe

hepatic impairment (see WARNINGS AND PRECAUTIONS, Special Populations, Hepatic Impairment).

Patients with Renal Impairment
Start patients on one-fourth to one-half the usual DILAUDID injection starting dose depending on the degree of impairment. Closely monitor patients with renal impairment for respiratory and central nervous system depression during initiation of therapy with DILAUDID and during dose titration (see WARNINGS AND PRECAUTIONS, Special Populations, Renal Impairment).

Geriatrics
Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. DILAUDID should be initiated at a low end of the dosing range and slowly titrated (see WARNINGS AND PRECAUTIONS).

Use with Non-Opioid Medications
If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. DILAUDID can be safely used concomitantly with usual doses of other non-opioid analgesics.

Dose Titration
Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at the regular administration of the lowest dose of DILAUDID which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response.

Adjustment or Reduction of Dosage
Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including DILAUDID. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Following successful relief of moderate to severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see WARNINGS AND PRECAUTIONS). Tapering should be individualized and carried out under medical supervision.

Patients should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Opioid analgesics may only be partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say

that patients with advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

4.3 Administration

Oral: DILAUDID tablets may be taken with a glass of water.

Parenteral: The usual adult parenteral dose for pain relief is administered by subcutaneous or intramuscular route every 4 to 6 hours as necessary. If necessary, HYDROmorphone may be given intravenously, but the injection should be given very slowly. Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression.

DILAUDID injection has been reported to be physically or chemically incompatible with solutions containing sodium bicarbonate and thiopental sodium.

4.4 Missed Dose

If the patient forgets to take one or more tablet doses, they should take their next dose at the next scheduled time and in the normal amount.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre immediately.

Symptoms
Serious overdosage with DILAUDID is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), dizziness, confusion, extreme somnolence progressing to stupor or coma, pneumonia aspiration, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, toxic leukoencephalopathy, delayed post-hypoxic leukoencephalopathy and sometimes bradycardia and hypotension. In severe overdosage, particularly following intravenous injection, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment
In the treatment of overdosage, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. It should be borne in mind that for individuals who are physically dependent on opioids and are receiving large doses of these drugs, the administration of the usual dose of opioid antagonist will precipitate an acute withdrawal syndrome. The severity will depend on the degree of physical dependence and the dose of the antagonist administered. Use of an opioid antagonist in such persons should be avoided. If necessary to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and by titration, commencing with 10 to 20% of the usual recommended initial dose.

Respiratory depression which may result from overdosage, or unusual sensitivity to HYDROmorphone in a non-opioid-tolerant patient, can be managed with the opioid antagonist naloxone. A dose of naloxone (usually 0.4 to 2.0 mg) should be administered intravenously, if

possible, simultaneously with respiratory resuscitation. The dose can be repeated in 3 minutes. Naloxone should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Naloxone should be administered cautiously to persons who are known or suspected to be physically dependent on HYDROmorphone. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome.

Since the duration of action of HYDROmorphone may exceed that of the antagonist, the patient should be kept under continued surveillance; repeated doses of the antagonist may be required to maintain adequate respiration. Other supportive measures should be applied when indicated.

Supportive measures, including oxygen and vasopressors, should be employed in the management of circulatory shock and pulmonary edema accompanying overdose, as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

Evacuation of gastric contents may be useful in removing unabsorbed drug, in particular when an oral formulation has been taken.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Immediate Release Tablets / 1 mg, 2 mg, 4 mg and 8 mg	Lactose anhydrous, magnesium stearate, D&C Yellow No. 10 Lake and FD&C Blue No. 1 Lake (for 1 mg), D&C Red No. 30 Lake and D&C Yellow No. 10 Lake (for 2 mg) and D&C Yellow No. 10 Lake (for 4 mg)
Intramuscular, Intravenous, Subcutaneous	Sterile Solution for Injection / 2 mg/mL	Citric acid, sodium citrate

Dosage Forms

Sterile solution for injection*:* Each mL of clear, colourless to pale yellow sterile solution contains: 2 mg HYDROmorphone hydrochloride. Non-medicinal ingredients: sodium citrate 2 mg, citric acid 2 mg. Preservative-free.

Tablets*:* Each tablet contains 1 mg HYDROmorphone hydrochloride (green), 2 mg HYDROmorphone hydrochloride (orange), 4 mg HYDROmorphone hydrochloride (yellow), or 8 mg HYDROmorphone hydrochloride (white, scored). Non-medicinal ingredients: lactose anhydrous and magnesium stearate. Also contains: D&C Yellow No. 10 Lake and FD&C Blue No. 1 Lake (for 1 mg), D&C Red No. 30 Lake and D&C Yellow No. 10 Lake (for 2 mg), D&C Yellow No. 10 Lake (for 4 mg). Tartrazine-free. Each tablet is debossed with the letter D on one side and the strength on the other. The 8 mg strength has the letter D on both sides of the score line.

Packaging

Sterile solution for injection*:* DILAUDID sterile solution for injection, containing 2 mg HYDROmorphone hydrochloride per mL, is available in 1 mL ampoules, boxes of 25.

***Tablets**:* DILAUDID tablets are available as green tablets of 1 mg; orange tablets of 2 mg; yellow tablets of 4 mg; or white, scored tablets of 8 mg. HYDROmorphone hydrochloride 1 mg, 2 mg, 4 mg and 8 mg tablets are available in bottles of 100 tablets and Hospital Control Packages of 4 x 25 tablets.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

Patients should be instructed not to give DILAUDID to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. DILAUDID should be stored securely to avoid theft or misuse.

DILAUDID should only be prescribed by healthcare professionals who are knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

In diseases, such as malignant cancers, where pain control is the primary focus, opioid administration at very high doses is associated with seizures and myoclonus.

If necessary, HYDROmorphone may be given intravenously but the injection should be given very slowly. Rapid intravenous injection of narcotic analgesic agents, including HYDROmorphone, increases the possibility of adverse effects, such as hypotension and respiratory depression.

Patients should be cautioned not to consume alcohol while taking DILAUDID as it may increase the chance of experiencing serious adverse events, including death (see DRUG INTERACTIONS).

Hyperalgesia that will not respond to a further dose increase of HYDROmorphone may occur at particularly high doses. A HYDROmorphone dose reduction or change in opioid may be required.

Addiction, Abuse and Misuse

Like all opioids, DILAUDID is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, DILAUDID should be prescribed and handled with caution. This risk is increased if DILAUDID is taken with alcohol or other CNS depressants.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as DILAUDID, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

DILAUDID tablets are intended for oral use only. The tablets should be swallowed whole, and not chewed or crushed. With parenteral abuse, the tablet excipients can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

Cardiovascular

Hypotension

HYDROmorphone administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedatives, hypnotics, tricyclic antidepressants or general anesthetics (see DRUG INTERACTIONS). These patients should be monitored for signs of hypotension after initiating or titrating the dose of DILAUDID.

The use of DILAUDID in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression and should be avoided (see DOSAGE AND ADMINISTRATION).

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of HYDROmorphone and there is a potential for development of psychological dependence. DILAUDID should therefore be prescribed and handled with the degree of caution appropriate to the use of a drug with abuse potential.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

Use in Drug and Alcohol Addiction

DILAUDID is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to DILAUDID; extreme caution and awareness is warranted to mitigate the risk.

Driving and Operating Machinery

HYDROmorphone may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of HYDROmorphone with other CNS depressants, including other opioids, phenothiazine, sedatives, hypnotics and alcohol.

Endocrine and Metabolism

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.

Gastrointestinal

HYDROmorphone and other morphine-like opioids have been shown to decrease bowel motility. HYDROmorphone may obscure the diagnosis or clinical course in patients with acute abdominal conditions and is also contraindicated in patients with paralytic ileus, appendicitis and pancreatitis. HYDROmorphone may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease for worsening symptoms (see CONTRAINDICATIONS and ADVERSE REACTIONS, Nausea and Vomiting and Constipation).

Neonatal Opioid Withdrawal Syndrome (NOWS)

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

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.

Use of DILAUDID is contraindicated in pregnant women (see CONTRAINDICATIONS).

Neurologic

Interactions with CNS Depressants (including benzodiazepines and alcohol)

HYDROmorphone should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

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). 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.

Advise both patients and caregivers about the risks of respiratory depression and sedation when DILAUDID is 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).

DILAUDID should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see CONTRAINDICATIONS and ADVERSE REACTIONS, Sedation, and DRUG INTERACTIONS).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

Use in Patients with Convulsive or Seizure Disorders
The HYDROmorphone in DILAUDID may aggravate convulsions in patients with convulsive disorders and may induce or aggravate seizures in some clinical settings. Therefore, DILAUDID should not be used in these patients (see CONTRAINDICATIONS).

Serotonin Toxicity / Serotonin Syndrome
Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has been reported with HYDROmorphone, including DILAUDID, particularly during combined use with other serotonergic drugs (see DRUG INTERACTIONS).

Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus.

If concomitant treatment with DILAUDID and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see DRUG INTERACTIONS). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Head Injury
The respiratory depressant effects of HYDROmorphone with carbon dioxide (CO_2) retention and the secondary elevation of cerebrospinal fluid pressure may be greatly increased in the presence of head injury, other intracranial lesions, or pre-existing increase in intracranial pressure. Opioid analgesics, including HYDROmorphone may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, DILAUDID should not be used (see CONTRAINDICATIONS).

Peri-Operative Considerations
DILAUDID is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with DILAUDID for at least 24 hours before the operation and DILAUDID tablets should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if DILAUDID is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

HYDROmorphone and other HYDROmorphone-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

DILAUDID tablets should not be used in the early post-operative period (12 to 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

Respiratory
Respiratory Depression
Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, 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. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. HYDROmorphone should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see CONTRAINDICATIONS).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of DILAUDID, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with DILAUDID and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

To reduce the risk of respiratory depression, proper dosing and titration of DILAUDID are essential. Overestimating the DILAUDID dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups, and DOSAGE AND ADMINISTRATION).

Use in Patients with Chronic Pulmonary Disease
Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with DILAUDID, as in these patients, even usual therapeutic doses of DILAUDID may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of DILAUDID is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see CONTRAINDICATIONS).

Sleep Apnea
Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids (see WARNINGS AND PRECAUTIONS, Dependence/Tolerance; DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

Sexual Health
Reproduction
Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see ADVERSE REACTIONS, Post-Market Adverse Reactions).

Patient Counselling Information
A patient information sheet should be provided to patients when DILAUDID is dispensed to them.

Patients receiving DILAUDID should be given the following instructions by the physician:

1. Patients should be informed that accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, may lead to severe, even fatal consequences. DILAUDID should be kept under lock and out of sight and out of reach of children.

2. Patients should be advised that DILAUDID contains HYDROmorphone, an opioid pain medicine.

3. Patients should be advised that DILAUDID should only be taken as directed. The dose of DILAUDID should not be adjusted without consulting with a physician. DILAUDID tablets

must be swallowed whole (not cut, broken, chewed, dissolved or crushed) due to the risk of fatal HYDROmorphone overdose.

4. Patients should not combine DILAUDID with alcohol or other central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.

5. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with DILAUDID.

6. Patients should be advised that if they have been receiving treatment with DILAUDID and cessation of therapy is indicated, it may be appropriate to taper DILAUDID dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.

7. Patients should be advised of the most common adverse reactions that may occur while taking DILAUDID: constipation, dizziness, light-headedness, nausea, sedation, sweating and vomiting. If symptoms worsen, seek immediate medical attention.

8. Patients should be advised that DILAUDID may cause drowsiness, dizziness or light-headedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on DILAUDID or patients whose dose has been adjusted should be advised not to drive a car or operate machinery unless they are tolerant to the effects of DILAUDID.

9. Patients should be advised that DILAUDID is a potential drug of abuse. They should protect it from theft or misuse.

10. Patients should be advised that DILAUDID should never be given to anyone other than the individual for whom it was prescribed.

11. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with DILAUDID. Women who are breast-feeding or pregnant should not use DILAUDID.

7.1 Special Populations

Special Risk Groups
HYDROmorphone should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

The administration of opioid analgesics, including HYDROmorphone, may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Opioid analgesics including HYDROmorphone should also be used with caution in patients about to undergo surgery of the biliary tract, since it may cause spasm of the sphincter of Oddi.

7.1.1 Pregnant Women

Studies in humans have not been conducted. DILAUDID crosses the placental barrier and is contraindicated in pregnant women (see CONTRAINDICATIONS).

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal Opioid Withdrawal Syndrome (NOWS), unlike opioid withdrawal syndrome in adults, may be life-threatening (see WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS) and ADVERSE REACTIONS, Post-Market Adverse Reactions).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complications such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

7.1.2 Breast-feeding

Since opioids can cross the placental barrier and are excreted in breast milk, DILAUDID is contraindicated in nursing women and during labour and delivery. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if DILAUDID is used in this population. Respiratory depression may occur in the infant if opioids are administered during labour. Therefore, DILAUDID should not be used during or immediately prior to labour or in nursing mothers.

7.1.3 Pediatrics (<18 years of age)

The safety and efficacy of DILAUDID has not been studied in the pediatric population. Therefore the use of DILAUDID is not recommended in patients under 18 years of age.

7.1.4 Geriatrics (>65 years of age)

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrated slowly, reflecting the greater frequency of decreased hepatic, renal or cardiac function, concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION).

7.1.5 Patients with Hepatic Impairment

The pharmacokinetics of HYDROmorphone following an oral administration of HYDROmorphone at a single 4 mg dose (2 mg HYDROmorphone immediate-release tablets) are affected by hepatic impairment. Mean exposure to HYDROmorphone (C_{max} and AUC_{∞}) is increased 4-fold in patients with moderate (Child-Pugh Group B) hepatic impairment compared with subjects with normal hepatic function. 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.

7.1.6 Patients with Renal Impairment

The pharmacokinetics of HYDROmorphone following an oral administration of HYDROmorphone at a single 4 mg dose (2 mg HYDROmorphone immediate-release tablets)

are affected by renal impairment. Mean exposure to HYDROmorphone (C_{max} and $AUC_{0-\infty}$) is increased by 2-fold in patients with moderate (CLcr = 40 - 60 mL/min) renal impairment and increased by 4-fold in patients with severe (CLcr < 30 mL/min) renal impairment compared with normal subjects (CLcr > 80 mL/min). In addition, in patients with severe renal impairment, HYDROmorphone appeared to be more slowly eliminated with a longer terminal elimination half-life (40 hr) compared to patients with normal renal function (15 hr). Patients with renal impairment should be closely monitored during dose titration.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The adverse effects of DILAUDID are similar to those of other opioid analgesics and represent an extension of pharmacological effects of the drug class. The major hazards include respiratory depression, central nervous system depression and apnea. To a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest have occurred.

The most frequently observed adverse effects are constipation, light-headedness, dizziness, sedation, nausea, vomiting, and hyperhidrosis.

Pain at injection site, local tissue irritation and induration following subcutaneous injection, particularly when repeated in the same area, have occurred.

Sedation
Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension particularly in elderly or debilitated patients and may be alleviated if the patient lies down.

Nausea and Vomiting
Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting prolonged therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation
Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid analgesic therapy. Stool softeners, stimulant laxatives and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

8.2 Adverse Reactions

The following adverse effects occur with opioid analgesics and include those reported in DILAUDID clinical trials, as well as post-marketing adverse events related to HYDROmorphone. The reactions are categorized by body system and frequency according to the following definitions: Very common (≥ 1/10); Common (≥ 1/100 to <1/10); Uncommon (≥ 1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

Immune System Disorders:
Not known: anaphylactic reactions, hypersensitivity reactions (including oropharyngeal swelling)

Metabolism and Nutrition Disorders:
Common: decreased appetite

Psychiatric Disorders:
Common: anxiety, confusional state, insomnia, euphoric mood, dysphoria
Uncommon: agitation, depression, hallucination, nightmares, mood altered
Not known: drug dependence, nervousness, disorientation

Nervous System Disorders:
Very common: dizziness, somnolence, sedation
Common: headache
Uncommon: myoclonus, paraesthesia, tremor, presyncope
Rare: lethargy
Not known: convulsions, dyskinesia, hyperalgesia, syncope, increased intracranial pressure, nystagmus, obstructive sleep apnea syndrome

Eye Disorders:
Uncommon: visual impairment
Not known: blurred vision, miosis, diplopia

Cardiac Disorders:
Rare: bradycardia, palpitations, tachycardia

Vascular Disorders:
Very common: flushing
Uncommon: hypotension
Not known: hypertension

Respiratory, Thoracic and Mediastinal Disorders:

Uncommon: dyspnea
Rare: respiratory depression
Not known: bronchospasm, and laryngospasm

Gastrointestinal Disorders:
Very common: constipation, nausea
Common: abdominal pain, dry mouth, vomiting
Uncommon: diarrhea, dysgeusia
Not known: paralytic ileus

Hepatobiliary Disorders:
Uncommon: hepatic enzymes increased
Not known: biliary colic

Skin and Subcutaneous Tissue Disorders:
Common: pruritus, hyperhidrosis
Uncommon: rash
Not known: urticaria

Musculoskeletal and Connective Tissue Disorders:
Common: muscle contractions involuntary
Not known: muscle rigidity

Renal and Urinary Disorders:
Uncommon: urinary retention, urinary hesitancy

Reproductive System and Breast Disorders:
Uncommon: erectile dysfunction

General Disorders and Administration Site Conditions:
Common: asthenia, injection site reaction, weakness
Uncommon: drug withdrawal syndrome, fatigue, malaise, peripheral edema
Not known: drug tolerance, chills, drug withdrawal syndrome neonatal, feeling abnormal

8.3 Post-Market Adverse Reactions

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.

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 (see WARNINGS AND PRECAUTIONS, Endocrine).

Anaphylaxis: Anaphylactic reaction has been reported with ingredients contained in DILAUDID.

***Androgen deficiency*:** 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. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

There have also been post-marketing reports of Neonatal Opioid Withdrawal Syndrome (NOWS) in patients treated with hydromorphone (see WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS)).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions Box

- Risks from concomitant use of opioids and benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS)
  - Reserve concomitant prescribing of DILAUDID and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate
  - Consider dose reduction of CNS depressants in situations of concomitant prescribing
  - Follow patients for signs and symptoms of respiratory depression and sedation
- MAO inhibitors intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. DILAUDID is contraindicated in patients receiving MAO inhibitors or who have used them within the previous 14 days.

9.2 Overview

Interactions with Central Nervous System (CNS) Depressants (including benzodiazepines and alcohol)
Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives, hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. 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 (see WARNINGS AND PRECAUTIONS, Neurologic, Interactions with CNS Depressants (including benzodiazepines and alcohol) and Driving and Operating Machinery). DILAUDID should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

9.3 Drug-Drug Interactions

Administration with Mixed Activity Agonist/Antagonist Opioids
Mixed agonist/antagonist opioid analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as HYDROmorphone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of HYDROmorphone and/or may precipitate withdrawal symptoms in these patients.

MAO Inhibitors
MAO Inhibitors intensify the effects of opioid drugs which can cause anxiety, confusion and decreased respiration. DILAUDID is contraindicated in patients receiving MAO inhibitors or who have used them within the previous 14 days (see CONTRAINDICATIONS).

HYDROmorphone may increase the anticoagulant activity of coumarin and other anticoagulants.

Serotonergic Agents
Coadministration of HYDROmorphone with a serotonergic agent, such as a selective serotonin re-uptake inhibitor (SSRI) or a serotonin norepinephrine re-uptake inhibitor (SNRI), may increase the risk of serotonin syndrome, a potentially life-threatening condition (see WARNINGS AND PRECAUTIONS, Neurologic).

9.4 Drug-Food Interactions

Interactions with food have not been established.

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9.7 Drug-Lifestyle Interactions

The concomitant use of alcohol should be avoided (see WARNINGS AND PRECAUTIONS, General).

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

DILAUDID (HYDROmorphone hydrochloride) has analgesic and antitussive activity. Small doses of HYDROmorphone produce effective and prompt relief of pain, usually with minimal nausea and vomiting.

Opioid analgesics have multiple actions but exert their primary effects on the central nervous system and organs containing smooth muscle. The principal actions of therapeutic value are analgesia and sedation. Opioid analgesics also suppress the cough reflex and cause respiratory depression, mood changes, mental clouding, euphoric mood, dysphoria, nausea, vomiting, increased cerebrospinal fluid pressure, pinpoint constriction of the pupils, increased biliary tract pressure, increased parasympathetic activity and transient hyperglycemia.

The precise mode of analgesic action of opioid analgesics is unknown. However, specific CNS opiate receptors have been identified. Opioids are believed to express their pharmacological effects by combining with these receptors.

10.2 Pharmacodynamics

When given parenterally, HYDROmorphone's analgesic action is generally apparent within five minutes. The onset of action of oral HYDROmorphone hydrochloride is somewhat slower, with measurable analgesia occurring within 30 minutes. When sleep follows the administration of HYDROmorphone, it is usually due to relief of pain, not to hypnosis.

Estimates of the relative analgesic potency of parenterally administered HYDROmorphone to morphine in acute pain studies in man range from approximately 7:1 to 11:1. In addition, HYDROmorphone is better absorbed orally than is morphine, the former approximately 20 to 25% as active orally as intramuscularly. HYDROmorphone has greater antitussive potency than codeine on a weight basis; however, its dependence liability is also greater than that of codeine.

Cardiovascular System
HYDROmorphone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

Central Nervous System
HYDROmorphone produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO_2 tension and to electrical stimulation.

HYDROmorphone depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

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

Endocrine System
Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

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 gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Hepatobiliary System
Opioids may induce biliary spasm.

Immune System
In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

10.3 Pharmacokinetics

Absorption: When HYDROmorphone is taken orally, it is absorbed from the gastrointestinal tract.

Distribution: Following intravenous administration of HYDROmorphone to normal volunteers, the mean $t_{1/2}$ of elimination was 2.65 +/- 0.88 hours. The mean volume of distribution was 91.5 liters, suggesting extensive tissue uptake. HYDROmorphone is rapidly removed from the bloodstream and distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. It also crosses the placental membranes.

Metabolism: In normal human volunteers HYDROmorphone is metabolized primarily in the liver.

Elimination: HYDROmorphone is excreted in the urine, predominantly as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. The pharmacologic activity of this and other HYDROmorphone metabolites in humans is not known.

Special Populations and Conditions
Pediatrics (<18 years of age): Individuals under 18 years of age should not take DILAUDID.

Geriatrics (>65 years of age): HYDROmorphone should be administered with caution, and in reduced dosages, to elderly or debilitated patients. Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. HYDROmorphone should be initiated at a low dose and slowly titrated to effect (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

Sex: No data available.

11 STORAGE, STABILITY AND DISPOSAL

Sterile Solution for Injection: Store DILAUDID sterile solution for injection at 15° to 25°C. Protect from light.

Tablets: Store DILAUDID tablets at 15° to 25°C. Keep in a dry place.

Disposal
DILAUDID should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired DILAUDID should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. DILAUDID should not be shared with others and steps should be taken to protect it from theft or misuse. The patient should speak to their pharmacist about temporary storage options, if required, until the medication can be returned to the pharmacy for safe disposal.

12 SPECIAL HANDLING INSTRUCTIONS

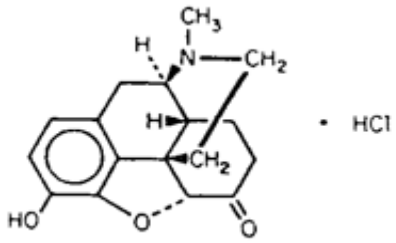
DILAUDID should be kept in a safe place, such as under lock and out of the sight and reach of children before, during and after use. DILAUDID should not be used in front of children, since they may copy these actions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

HYDROmorphone is a semisynthetic congener of morphine, differing structurally from morphine in the substitution of an oxygen for the 6-hydroxyl group and hydrogenation of the 7-8 double bond of the morphine molecule.

Proper name:	HYDROmorphone hydrochloride
Chemical name:	4,5α-Epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride
Molecular formula and molecular mass:	$C_{17}H_{19}NO_3 \cdot HCl$ / 321.8
Structural formula:	
Physicochemical Properties:	HYDROmorphone hydrochloride is a hydrogenated ketone of morphine.
Appearance:	Fine, white, or practically white, crystalline powder.
Solubility:	Soluble 1:3 in water and 1:100 in alcohol (90%); practically insoluble in chloroform and ether.
Melting Point:	Decomposes at 305° to 315°C.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[N]DILAUDID®

(HYDROmorphone Hydrochloride)
Tablets and Sterile Solution for Injection

Read this carefully before you start taking DILAUDID and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about DILAUDID.

Serious Warnings and Precautions

- Even if you take DILAUDID as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death. To understand your risk of opioid addiction, abuse, and misuse you should speak to your prescriber (e.g., doctor).
- When you take DILAUDID tablets they must be swallowed whole. Do not cut, break, crush, chew, or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.
- Life-threatening breathing problems can happen while taking DILAUDID, especially if not take as directed. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.
- Never give anyone your DILAUDID. They could die from taking it. If a person has not been prescribed DILAUDID, taking even one dose can cause a fatal overdose. This is especially true for children.
- If you took DILAUDID while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:
    - has changes in their breathing (such as weak, difficult or fast breathing)
    - is unusually difficult to comfort
    - has tremors (shakiness)
    - has increased stools, sneezing, yawning, vomiting, or fever

  Seek immediate medical help for your baby.
- Taking DILAUDID 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.

What is DILAUDID used for?
DILAUDID is a pain medication used to control pain.

How does DILAUDID work?
DILAUDID contains HYDROmorphone which is a pain medication belonging to the class of drugs known as opioids which includes codeine, fentanyl, morphine and oxycodone. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

DILAUDID Injection is used to treat severe pain in patients who need an opioid administered by injection. This is given under the skin, into the muscle or vein in doses or concentrations that are higher than those usually needed.

What are the ingredients in DILAUDID?
Medicinal ingredient: HYDROmorphone hydrochloride
Non-medicinal ingredients in tablet: lactose anhydrous, magnesium stearate.

In addition, the tablet strengths listed below contain the following dyes:
1 mg: D&C Yellow No.10 Lake, FD&C Blue No. 1 Lake
2 mg: D&C Red No. 30 Lake, D&C Yellow No. 10 Lake
4 mg: D&C Yellow No. 10 Lake

Non-medicinal ingredients in sterile solution for injection: sodium citrate, citric acid

DILAUDID comes in the following dosage forms:
Immediate Release Tablets: 1 mg, 2 mg, 4 mg and 8 mg.
Sterile solution for injection: 2 mg/mL.

Do not use DILAUDID if:
- your doctor did not prescribe it for you
- you are allergic to HYDROmorphone, or any of the other ingredients in DILAUDID tablets or injection (see What are the ingredients in DILAUDID?)
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you have a brain tumor
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase Inhibitor (MOI) (such as phenelzine sulfate, tranylcypromine sulfate, moclobemide or selegiline)
- you are going to have, or recently had, a planned surgery
- you are pregnant or planning to become pregnant or you are in labour
- you are breastfeeding

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DILAUDID. Talk about any health conditions or problems you may have, including if you:
- have a history of illicit or prescription drug or alcohol abuse
- have severe kidney, liver or lung disease
- have heart disease
- have low blood pressure

- have a history of sleep apnea
- have past or current depression
- suffer from chronic or severe constipation
- have problems with your adrenal or prostate gland
- have, or had in the past, hallucinations or other severe mental problems
- suffer from migraines
- are pregnant or planning to become pregnant

Other warnings you should know about:

Opioid dependence and addiction
There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

Pregnancy, nursing, labour, and delivery
Do not use DILAUDID while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. DILAUDID can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking DILAUDID**,** it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your doctor will monitor and guide you on how to slowly stop taking DILAUDID**.** This may help avoid serious harm to your unborn baby.

Driving and using machines
Before you do tasks which may require special attention, you should wait until you know how you react to DILAUDID. DILAUDID can cause:
- drowsiness
- dizziness or
- light-headedness

This can usually occur after you take your first dose and when your dose is increased.

Disorder of the adrenal gland
You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:
- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off DILAUDID**.**

Serotonin Syndrome
DILAUDID can cause serotonin syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin syndrome if you take DILAUDID with certain anti-depressants or migraine medications.

Serotonin syndrome symptoms include:
- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Sexual Function/Reproduction
Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Sleep Apnea
Opioids can cause a problem called sleep apnea (stopping breathing from time to time while sleeping). Tell your doctor if you have a history of sleep apnea or if anyone notices that you stop breathing from time to time while sleeping.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with DILAUDID:
- alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking DILAUDID. It can lead to:
  - drowsiness
  - unusually slow or weak breathing
  - serious side effects or
  - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by DILAUDID
- other opioid analgesics (for pain)
- general anesthetics (used during surgery)
- drugs used to help you sleep or that help reduce anxiety (benzodiazepines)
- antidepressants (for depression and mood disorders). **Do not** take DILAUDID with monoamine oxidase (MAO) inhibitors or if you have taken MAO inhibitors in the last 14 days before treatment with DILAUDID
- drugs used to treat serious mental or emotional disorders, such as schizophrenia
- antihistamines (for allergies)
- anti-emetics (for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- some heart medications (such as beta blockers)
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

How to take DILAUDID:
Take DILAUDID tablets and injection:
- usually every 4 to 6 hours, or as directed by your doctor
- with a full glass of water

DILAUDID tablets**:**
Swallow whole. Do not cut, break, crush, chew or dissolve the tablet. This can be

dangerous and can lead to death or seriously harm you.

DILAUDID injection:
Should be visually inspected prior to use. Only clear solutions free from particles should be used. The injection should be given immediately after opening the ampoule. Once opened, any unused portion should be discarded.

Usual Dose:
Your dose is tailored/personalized just for you. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor.

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take DILAUDID for up to 7 days. If you need to take DILAUDID for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your doctor to determine if you still need DILAUDID. Be sure to use DILAUDID only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking DILAUDID, tell your doctor immediately.

Stopping your Medication:
If you have been taking DILAUDID for more than a few days you should not stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking DILAUDID. You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebumps
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- having trouble sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness
- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking DILAUDID.

Refilling your Prescription for DILAUDID:
A new written prescription is required from your doctor each time you need more DILAUDID. Therefore, it is important that you contact your doctor before your current supply runs out.

Only obtain prescriptions for this medication from the doctor in charge of your treatment. Do not seek prescriptions from other doctors unless you switch to another doctor for your pain management.

Overdose:

If you think you have taken too much DILAUDID, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Signs of overdose may include:
- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

Missed Dose:
If you miss one tablet dose, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once. If you miss several doses in a row, talk to your doctor before restarting your medication.

What are possible side effects from using DILAUDID?
These are not all the possible side effects you may feel when taking DILAUDID. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:
- drowsiness
- insomnia
- dizziness
- fainting
- nausea, vomiting, or a poor appetite
- dry mouth
- headache
- problems with vision
- weakness, uncoordinated muscle movement
- lack of muscle strength
- itching
- light-headedness
- sweating
- constipation
- confusion
- anxiety
- abdominal pain
- injection site reaction
- low sex drive, impotence (erectile dysfunction), infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using DILAUDID.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin.			✓
Respiratory Depression: slow, shallow or weak breathing.			✓
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			✓
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea.			✓
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		✓	
Fast, Slow or Irregular Heartbeat: heart palpitations.		✓	
Low Blood Pressure: dizziness, fainting, light-headedness.	✓		
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting/drug.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- **Keep unused or expired DILAUDID in a secure place to prevent theft, misuse or accidental exposure.**
- Store tablets and sterile solution for injection at room temperature (15°- 25°C). Keep in a dry place. Protect sterile solution for injection from light.
- **Keep DILAUDID under lock, out of sight and reach of children and pets.**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes DILAUDID, get emergency help right away.**

Disposal:

DILAUDID should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about DILAUDID:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.purdue.ca, or by calling 1-800-387-4501.

This leaflet was prepared by Purdue Pharma.

Last Revised: July 7, 2021