

DILAUDID[®] and DILAUDID-HP[®] INJECTION

1 mg/mL, 2 mg/mL, 4mg/mL, and 10 mg/mL

(hydromorphone hydrochloride)

C-II

WARNING: DILAUDID-HP[®] (high potency, 10 mg/mL ampules and vials) is a more concentrated solution of hydromorphone than DILAUDID[®] INJECTION, and is intended for use only in opioid-tolerant patients. Do not confuse DILAUDID-HP with standard parenteral formulations of DILAUDID or other opioids, as overdose and death could result.

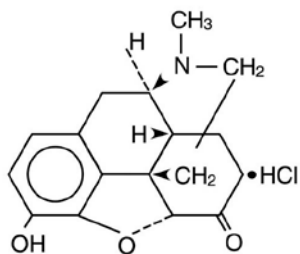
DILAUDID INJECTION (1, 2, and 4 mg/mL ampules, sterile solution for parenteral administration) and DILAUDID-HP contain hydromorphone, a potent Schedule II opioid agonist.

Schedule II opioid agonists, including morphine, oxycodone, hydromorphone, oxycodone, fentanyl and methadone, have the highest potential for abuse and risk of producing respiratory depression. Ethanol, other opioids, and other central nervous system depressants (e.g., sedative-hypnotics, skeletal muscle relaxants) can potentiate the respiratory-depressant effects of hydromorphone and increase the risk of adverse outcomes, including death.

DESCRIPTION

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

The chemical name of DILAUDID (hydromorphone hydrochloride) is 4,5 α -epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride. The structural formula is:



M.W. 321.8

DILAUDID INJECTION is available in ampules for parenteral administration. Each 1 mL of sterile aqueous solution contains 1 mg, 2 mg, or 4 mg hydromorphone hydrochloride with 0.2% sodium citrate and 0.2% citric acid solution. DILAUDID INJECTION ampules are sterile. HIGH POTENCY DILAUDID (DILAUDID-HP) is available in AMBER ampules or single dose vials for intravenous (IV), subcutaneous (SC), or intramuscular (IM) administration. Each 1 mL of sterile aqueous solution contains 10 mg hydromorphone hydrochloride with 0.2% sodium citrate and 0.2% citric acid solution.

It is also available as lyophilized DILAUDID-HP for intravenous (IV), subcutaneous (SC), or intramuscular (IM) administration. Each single dose vial contains 250 mg sterile, lyophilized hydromorphone HCl to be reconstituted with 25 mL of Sterile Water for Injection USP to provide a solution containing 10 mg/mL. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

CLINICAL PHARMACOLOGY

Hydromorphone hydrochloride is a pure opioid agonist with the principal therapeutic activity of analgesia. A significant feature of the analgesia is that it can occur without loss of consciousness. Opioid analgesics also suppress the cough reflex and may cause respiratory depression, mood changes, mental clouding, euphoria, dysphoria, nausea, vomiting and electroencephalographic changes. Many of the effects described below are common to the class of mu-opioid analgesics, which includes morphine, oxycodone, hydrocodone, codeine, and fentanyl. In some instances, data may not exist to demonstrate that DILAUDID INJECTION and DILAUDID-HP possess similar or different effects than those observed with other opioid analgesics. However, in the absence of data to the contrary, it is assumed that DILAUDID INJECTION and DILAUDID-HP would possess these effects.

Central Nervous System

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.

Hydromorphone depresses the cough reflex by direct effect on the cough center in the medulla.

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

Hydromorphone causes miosis. Pinpoint pupils are a common 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 DILAUDID INJECTION or DILAUDID-HP overdose.

Gastrointestinal Tract and Other Smooth Muscle

Gastric, biliary and pancreatic secretions are decreased by opioids such as hydromorphone. Hydromorphone causes a reduction in motility associated with an increase in tone in the gastric antrum and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, and tone may be increased to the point of spasm. The end result is constipation. Hydromorphone can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi.

Cardiovascular System

Hydromorphone may produce hypotension as a result of either peripheral vasodilation, release of histamine, or both. Other manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, and red eyes.

Effects on the myocardium after intravenous administration of opioids are not significant in normal persons, vary with different opioid analgesic agents and vary with the hemodynamic state of the patient, state of hydration and sympathetic drive.

Pharmacokinetics and Metabolism

Distribution

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

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.

Elimination

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. 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.

Special Populations

Hepatic Impairment

After oral administration of hydromorphone at a single 4 mg dose (2 mg Dilaudid IR Tablets), mean exposure to hydromorphone (C_{max} and AUC_{∞}) is increased 4 fold in patients with moderate (Child-Pugh Group B) hepatic impairment compared with subjects with normal hepatic function. Due to increased exposure of hydromorphone, patients with moderate hepatic impairment should be started at a lower dose 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. As such, the starting dose should be even more conservative (see **DOSAGE AND ADMINISTRATION**).

Renal Impairment

After oral administration of hydromorphone at a single 4 mg dose (2 mg Dilaudid IR Tablets), mean exposure to hydromorphone (C_{max} and AUC_{0-48}) is increased in patients with impaired renal function by 2-fold, in moderate ($CL_{cr} = 40 - 60$ mL/min) renal impairment 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 a 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 **DOSAGE AND ADMINISTRATION**).

Pediatrics

Pharmacokinetics of hydromorphone have not been evaluated in children.

Geriatric

The effect of age on the pharmacokinetics of hydromorphone has not been adequately evaluated.

Gender

Gender has little effect on the pharmacokinetics of hydromorphone. Females appear to have a higher C_{max} (25%) than males with comparable AUC_{0-24} values. The difference observed in C_{max} may not be clinically relevant.

Pregnancy and Nursing Mothers

Hydromorphone crosses the placenta. Hydromorphone is also found in low levels in breast milk, and may cause respiratory compromise in newborns when administered during labor or delivery.

CLINICAL TRIALS

Analgesic effects of single doses of DILAUDID ORAL LIQUID 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 LIQUID provided significantly more analgesia than placebo.

INDICATIONS AND USAGE

DILAUDID INJECTION is indicated for the management of pain in patients where an opioid analgesic is appropriate.

DILAUDID-HP is indicated for the relief of moderate-to-severe pain in opioid-tolerant patients who require larger than usual doses of opioids to provide adequate pain relief. Because DILAUDID-HP contains 10 mg of hydromorphone hydrochloride per mL, a smaller injection volume can be used than with other parenteral opioid formulations. Discomfort associated with the intramuscular or subcutaneous injection of an unusually large volume of solution can therefore be avoided.

CONTRAINDICATIONS

DILAUDID INJECTION and DILAUDID-HP are contraindicated in patients with known hypersensitivity to hydromorphone.

DILAUDID INJECTION and DILAUDID-HP are contraindicated in patients with respiratory depression in the absence of resuscitative equipment and in patients with status asthmaticus.

DILAUDID INJECTION and DILAUDID-HP are also contraindicated for use in obstetrical analgesia.

DILAUDID-HP is contraindicated in patients who are not already receiving large amounts of opioids.

WARNINGS

DILAUDID-HP (high potency, 10 mg/mL ampules and vials) is a more concentrated solution of hydromorphone than DILAUDID INJECTION, and is intended for use only in opioid-tolerant patients. Do not confuse DILAUDID-HP with standard parenteral formulations of DILAUDID or other opioids, as overdose and death could result.

Respiratory Depression

Respiratory depression is the chief hazard of DILAUDID INJECTION and DILAUDID-HP. Respiratory depression occurs most frequently in the elderly, in the debilitated, and in those suffering from conditions accompanied by hypoxia or hypercapnia, or upper airway obstruction, in whom even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

DILAUDID INJECTION and DILAUDID-HP should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients even usual therapeutic doses of opioid analgesics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. Alternative non-opioid analgesics should be considered, and DILAUDID should be employed only under careful medical supervision at the lowest effective dose in such patients.

Misuse, Abuse, and Diversion of Opioids

DILAUDID INJECTION and DILAUDID-HP contain hydromorphone, an opioid agonist of the morphine-type, which is a potent Schedule II, controlled substance. Schedule II opioid agonists, including morphine, oxycodone, oxymorphone, fentanyl and methadone, have the highest potential for abuse and risk of fatal respiratory depression. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

DILAUDID INJECTION and DILAUDID-HP can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing DILAUDID INJECTION or DILAUDID-HP in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Prescribers should monitor all patients receiving opioids for signs of abuse, misuse, and addiction. Furthermore, patients should be assessed for their potential for opioid abuse prior to being prescribed opioid therapy. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse) or mental illness (e.g., depression).

Opioids may still be appropriate for use in these patients, however, they will require intensive monitoring for signs of abuse.

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Alcohol, other opioids and central nervous system depressants (sedative-hypnotics) potentiate the respiratory depressant effects of hydromorphone, increasing the risk of respiratory depression that might result in death.

Neonatal Withdrawal Syndrome

Infants born to mothers physically dependent on DILAUDID INJECTION or DILAUDID-HP will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms. (see **DRUG ABUSE AND DEPENDENCE**).

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of DILAUDID INJECTION and DILAUDID-HP with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or preexisting increase in intracranial pressure. Opioid analgesics including DILAUDID INJECTION and DILAUDID-HP may produce effects on pupillary response and consciousness which can obscure the clinical course and neurologic signs of further increase in pressure in patients with head injuries.

Hypotensive Effect

Opioid analgesics, including DILAUDID INJECTION and DILAUDID-HP, may cause severe hypotension in an individual whose ability to maintain his blood pressure has already been compromised by a depleted blood volume, or a concurrent administration of drugs such as phenothiazines or general anesthetics (see **PRECAUTIONS - Drug Interactions**). DILAUDID INJECTION and DILAUDID-HP may produce orthostatic hypotension in ambulatory patients.

DILAUDID INJECTION and DILAUDID-HP should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Sulfites

DILAUDID INJECTION and DILAUDID-HP 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.

PRECAUTIONS

General

Because of its high concentration, the delivery of precise doses of DILAUDID-HP may be difficult if low doses of hydromorphone are required. Therefore, DILAUDID-HP should be used only if the amount of hydromorphone required can be delivered accurately with this formulation.

Gastrointestinal Effects

DILAUDID INJECTION and DILAUDID-HP should not be administered to patients with gastrointestinal obstruction, especially paralytic ileus, because hydromorphone diminishes the propulsive peristaltic wave in the gastrointestinal tract and may prolong the obstruction.

The administration of DILAUDID INJECTION or DILAUDID-HP may obscure the diagnosis or clinical course in patients with acute abdominal condition.

Use in Pancreatic/Biliary Tract Disease

DILAUDID INJECTION and DILAUDID-HP should be used with caution in patients with biliary tract disease, including acute pancreatitis, as hydromorphone may cause spasm of the sphincter of Oddi and diminish biliary and pancreatic secretions.

Special Risk Patients

DILAUDID INJECTION and DILAUDID-HP should be given with caution and the initial dose should be reduced in the elderly or debilitated and those with severe impairment of hepatic, pulmonary or renal function; myxedema or hypothyroidism; adrenocortical insufficiency (e.g., Addison's Disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

In the case of DILAUDID-HP, however, the patient is presumed to be receiving an opioid to which he or she exhibits tolerance and the initial dose of DILAUDID-HP selected should be estimated based on the relative potency of hydromorphone and the opioid previously used by the patient. (see **DOSAGE AND ADMINISTRATION**).

The administration of opioid analgesics including DILAUDID INJECTION and DILAUDID-HP may aggravate preexisting convulsions in patients with convulsive disorders.

Reports of mild to severe seizures and myoclonus have been reported in severely compromised patients, administered high doses of parenteral hydromorphone, for cancer and severe pain. Opioid administration at very high doses is associated with seizures and myoclonus in a variety of diseases where pain control is the primary focus.

Use in Drug and Alcohol Dependent Patients

DILAUDID INJECTION and DILAUDID-HP should be used with caution in patients with alcoholism and other drug dependencies due to the increased frequency of opioid tolerance, dependence, and the risk of addiction observed in these patient populations. Abuse of DILAUDID INJECTION or DILAUDID-HP in combination with other CNS depressant drugs can result in serious risk to the patient.

Hydromorphone is an opioid with no approved use in the management of addictive disorders.

Driving and Operating Machinery

DILAUDID INJECTION and DILAUDID-HP may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g. driving, operating machinery). Patients should be cautioned accordingly. DILAUDID INJECTION and DILAUDID-HP may produce orthostatic hypotension in ambulatory patients.

Tolerance and Physical Dependence

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). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, mydriasis. Other 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.

In general, opioids used regularly should not be abruptly discontinued.

Information for Patients/Caregivers

Patients receiving DILAUDID (hydromorphone hydrochloride) or their caregivers should be given the following information by the physician, nurse, or pharmacist:

1. Patients should be aware that DILAUDID INJECTION and DILAUDID-HP contain hydromorphone, which is a morphine-like substance and which could cause severe adverse effects including respiratory depression and even death if not taken according to the prescriber's directions.
2. Patients should be advised to report pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
3. Patients should be advised not to adjust the dose of DILAUDID INJECTION or DILAUDID-HP without consulting the prescribing professional.

4. Patients should be advised that DILAUDID INJECTION and DILAUDID-HP may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
5. Patients should not combine DILAUDID INJECTION or DILAUDID-HP with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
6. Women of childbearing potential who become, or are planning to become pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
7. Patients should be advised that DILAUDID INJECTION and DILAUDID-HP are potential drugs of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
8. Patients should be advised that if they have been receiving treatment with DILAUDID INJECTION or DILAUDID-HP for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the DILAUDID INJECTION or DILAUDID-HP dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
9. Patients should be instructed to keep DILAUDID INJECTION and DILAUDID-HP in a secure place out of the reach of children.

Drug Interactions

Drug Interactions with other CNS Depressants

The concomitant use of other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers and alcohol may produce additive depressant effects. Respiratory depression, hypotension and profound sedation or coma may occur. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Opioid analgesics, including DILAUDID INJECTION and DILAUDID-HP, may enhance the action of neuromuscular blocking agents and produce an increased degree of respiratory depression.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist 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.

Parenteral Administration

DILAUDID INJECTION may be given intravenously, but the injection should be given very slowly. Rapid intravenous injection of opioid analgesics increases the possibility of side effects such as hypotension and respiratory depression.

Reports of mild to severe seizures and myoclonus have been reported in severely compromised patients, administered high doses of parenteral hydromorphone, for cancer and severe pain. Opioid administration at very high doses is associated with seizures and myoclonus in a variety of diseases where pain control is the primary focus.

Experience with administration of DILAUDID-HP by the intravenous route is limited. Should intravenous administration be necessary, the injection should be given slowly, over at least 2 to 3 minutes.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted in animals.

Hydromorphone was not mutagenic in the *in vitro* Ames reverse mutation assay, or the human lymphocytes chromosome aberration assay. Hydromorphone was not clastogenic in the *in vivo* mouse micronucleus assay.

No effects on fertility, reproductive performance, or reproductive organ morphology were observed in male or female rats given oral doses up to 7 mg/kg/day which is equivalent to and 3-fold higher than the human dose of DILAUDID-HP when substituted for ORAL LIQUID or 8 mg TABLET, respectively, on a body surface area basis.

PREGNANCY

PREGNANCY CATEGORY C

No effects on teratogenicity or embryotoxicity were observed in female rats given oral doses up to 7 mg/kg/day which is equivalent to and 3-fold higher than the human dose of DILAUDID-HP, on a body surface area basis. Hydromorphone produced skull malformations (exencephaly and cranioschisis) in Syrian hamsters given oral doses up to 20 mg/kg during the peak of organogenesis (gestation days 8-9). The skull malformations were observed at doses approximately 2-fold and 7-fold higher than the human dose of DILAUDID-HP when substituted for ORAL LIQUID or 8 mg TABLET, respectively, on a body surface area basis. There are no adequate and well-controlled studies of DILAUDID INJECTION or DILAUDID-HP in pregnant women.

Hydromorphone crosses the placenta, resulting in fetal exposures. DILAUDID INJECTION or DILAUDID-HP should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus (see **Labor and Delivery** and **DRUG ABUSE AND DEPENDENCE**).

Nonteratogenic Effects

Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes,

increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal. Approaches to the treatment of this syndrome have included supportive care and, when indicated, drugs such as paregoric or phenobarbital.

Labor and Delivery

DILAUDID INJECTION and DILAUDID-HP are contraindicated in Labor and Delivery (see **CONTRAINDICATIONS**).

Nursing Mothers

Low levels of opioid analgesics have been detected in human milk. As a general rule, nursing should not be undertaken while a patient is receiving DILAUDID INJECTION or DILAUDID-HP since it, and other drugs in this class, may be excreted in the milk.

Pediatric Use

Safety and effectiveness have not been established.

Geriatric Use

Clinical studies of DILAUDID INJECTION and DILAUDID-HP did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, 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. (see **DOSAGE AND ADMINISTRATION - Individualization Of Dosage and PRECAUTIONS**).

ADVERSE REACTIONS

The major hazards of DILAUDID INJECTION and DILAUDID-HP include respiratory depression and apnea. To a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest have occurred.

The most frequently observed 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

General and CNS

Weakness, headache, agitation, tremor, uncoordinated muscle movements, alterations of mood (nervousness, apprehension, depression, floating feelings, dreams), muscle rigidity, paresthesia, muscle tremor, blurred vision, nystagmus, diplopia and miosis, transient hallucinations and disorientation, visual disturbances, insomnia, increased intracranial pressure

Cardiovascular

Flushing of the face, chills, tachycardia, bradycardia, palpitation, faintness, syncope, hypotension, hypertension

Respiratory

Bronchospasm and laryngospasm

Gastrointestinal

Constipation, biliary tract spasm, ileus, anorexia, diarrhea, cramps, taste alterations

Genitourinary

Urinary retention or hesitancy, antidiuretic effects

Dermatologic

Urticaria, other skin rashes, wheal and flare over the vein with intravenous injection, diaphoresis

Other

In clinical trials, neither local tissue irritation nor induration was observed at the site of subcutaneous injection of DILAUDID-HP; pain at the injection site was rarely observed.

OVERDOSAGE

Acute overdosage with DILAUDID INJECTION or DILAUDID-HP is characterized by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes bradycardia and hypotension. In serious overdosage, particularly following intravenous injection, apnea, circulatory collapse, cardiac arrest and death may occur.

Hydromorphone may cause 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 overdose situations.

In the treatment of overdosage, primary attention should be given to the reestablishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen, 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.

The opioid antagonist, naloxone, is a specific antidote against respiratory depression which may result from overdosage, or unusual sensitivity to DILAUDID INJECTION or DILAUDID-HP. Therefore, an appropriate dose of this antagonist should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Naloxone should not be administered in the

absence of clinically significant respiratory or circulatory depression. Naloxone should be administered cautiously to persons who are known, or suspected to be physically dependent on DILAUDID INJECTION or DILAUDID-HP. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

Since the duration of action of DILAUDID INJECTION and DILAUDID-HP 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. Apply other supportive measures when indicated.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to hydromorphone overdose. Such agents 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. In an individual physically dependent on opioids, administration of the usual dose 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. Use of an opioid antagonist should be reserved for cases where such treatment is clearly needed. If it is necessary to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and titrated with smaller than usual doses.

DOSAGE AND ADMINISTRATION

DILAUDID INJECTION

The usual starting dose is 1-2 mg *subcutaneously* or *intramuscularly* every 4 to 6 hours as necessary for pain control. The dose should be adjusted according to the severity of pain, as well as the patient's underlying disease, age, and size. Patients with terminal cancer may be tolerant to opioid analgesics and may, therefore, require higher doses for adequate pain relief. Intravenous or subcutaneous administration is usually not painful. Should intravenous administration be necessary, the injection should be given slowly, over at least 2 to 3 minutes, depending on the dose. A gradual increase in dose may be required if analgesia is inadequate, tolerance occurs, or if pain severity increases. The first sign of tolerance is usually a reduced duration of effect.

Patients with hepatic and renal impairment should be started on a lower starting dose (see **CLINICAL PHARMACOLOGY - Pharmacokinetics and Metabolism**).

If DILAUDID INJECTION is substituted for a different opioid analgesic, the equivalency tables below should be used as a guide to determine the appropriate dose of DILAUDID INJECTION.

DILAUDID-HP

DILAUDID-HP SHOULD BE GIVEN ONLY TO PATIENTS WHO ARE ALREADY RECEIVING LARGE DOSES OF OPIOIDS. DILAUDID-HP is indicated for relief of moderate-to-severe pain in opioid-tolerant patients. Thus, these patients will already have been treated with other opioid analgesics. If the patient is being changed from regular DILAUDID to DILAUDID-HP, similar doses should be used, depending on the

patient's clinical response to the drug. If DILAUDID-HP is substituted for a different opioid analgesic, the following equivalency table should be used as a guide to determine the appropriate dose of DILAUDID-HP. Patients with hepatic and renal impairment should be started on a lower starting dose (see **CLINICAL PHARMACOLOGY - Pharmacokinetics and Metabolism**).

OPIOID ANALGESIC EQUIVALENTS WITH APPROXIMATELY EQUIANALGESIC POTENCY*

Drug Substance	IM or SC** Dose	Oral Dose
Morphine Sulfate	10 mg	40 – 60 mg
Hydromorphone HCl	1.3 – 2 mg	6.5 – 7.5 mg
Oxymorphone HCl	1 – 1.1 mg	6.6 mg
Levorphanol tartrate	2 – 2.3 mg	4 mg
Meperidine HCl (pethidine HCl)	75 – 100 mg	300 – 400 mg
Methadone HCl	10 mg	10 – 20 mg
Nalbuphine HCl	12 mg	---
Butorphanol tartrate	1.5 – 2.5 mg	---

* Dosages, and ranges of dosages represented, are a compilation of estimated equipotent dosages from published references comparing opioid analgesics in cancer and severe pain.

** IM = intramuscular; SC = subcutaneous

Experience with administration of DILAUDID-HP by the intravenous route is limited. Should intravenous administration be necessary, the injection should be given slowly, over at least 2 to 3 minutes.

A gradual increase in dose may be required if analgesia is inadequate, tolerance occurs, or if pain severity increases. The first sign of tolerance is usually a reduced duration of effect.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. A slight yellowish discoloration may develop in DILAUDID INJECTION and DILAUDID-HP ampules. No loss of potency has been demonstrated. DILAUDID INJECTION and DILAUDID-HP injection are physically compatible and chemically stable for at least 24 hours at 25°C protected from light in most common large volume parenteral solutions.

500 mg/50 mL Vial*

To use this single dose presentation, do not penetrate the stopper with a syringe. Instead, remove both the aluminum flipseal and rubber stopper in a suitable work area such as under a laminar flow hood (or equivalent clean air compounding area). The contents may then be withdrawn for preparation of a single, large volume parenteral solution. Any unused portion should be discarded in an appropriate manner.

Reconstitution of Sterile Lyophilized DILAUDID-HP 250 mg*

Reconstitute immediately prior to use with 25 mL of Sterile Water for Injection USP to provide a sterile solution containing 10 mg/mL.

***The Packaging Of These Products Contain Dry Natural Rubber.**

Individualization Of Dosage

The dosage of opioid analgesics like hydromorphone hydrochloride should be individualized for any given patient, since adverse events can occur at doses that may not provide complete freedom from pain.

Safe and effective administration of opioid analgesics to patients with acute or chronic pain depends upon a comprehensive assessment of the patient. The nature of the pain (severity, frequency, etiology, and pathophysiology), as well as the concurrent medical status of the patient, will affect selection of the starting dosage.

In patients receiving opioids, both the dose and duration of analgesia will vary substantially depending on the patient's opioid tolerance. The dose should be selected and adjusted so that at least 3-4 hours of pain relief may be achieved. In patients taking opioid analgesics, the starting dose of DILAUDID INJECTION or DILAUDID-HP should be based on prior opioid usage. This should be done by converting the total daily usage of the previous opioid to an equivalent total daily dosage of DILAUDID INJECTION or DILAUDID-HP using an equianalgesic table (see above). For opioids not in the table, first estimate the equivalent total daily usage of oral morphine, then use the table to find the equivalent total daily dosage of DILAUDID INJECTION or DILAUDID-HP.

Once the total daily dosage of DILAUDID INJECTION or DILAUDID-HP has been estimated, it should be divided into the desired number of doses. Since there is individual variation in response to different opioid drugs, only 1/2 to 2/3 of the estimated dose of DILAUDID INJECTION or DILAUDID-HP calculated from equivalence tables should be given for the first few doses, then increased as needed according to the patient's response.

Since the pharmacokinetics of hydromorphone are affected in hepatic and renal impairment with a consequent increase in exposure, patients with hepatic and renal impairment should be started on a lower starting dose (see **CLINICAL PHARMACOLOGY - Pharmacokinetics and Metabolism**).

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

Periodic reassessment after the initial dosing is always required. If pain management is not satisfactory, and in the absence of significant opioid-induced adverse events, the hydromorphone dose may be increased gradually. If excessive opioid side effects are observed early in the dosing interval, the hydromorphone hydrochloride dose should be reduced. If this results in breakthrough pain at the end of the dosing interval, the dosing interval may need to be shortened. Dose titration should be guided more by the need for analgesia than the absolute dose of opioid employed.

DRUG ABUSE AND DEPENDENCE

DILAUDID INJECTION and DILAUDID-HP contain hydromorphone, a Schedule II controlled opioid agonist. Schedule II opioid substances which include morphine, oxycodone, oxymorphone, fentanyl,

and methadone have the highest potential for abuse and risk of fatal overdose. Hydromorphone can be abused and is subject to criminal diversion.

Opioid analgesics may cause psychological and physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage, but it may occur after as little as a week of opioid use. Physical dependence and tolerance are separate and distinct from abuse and addiction.

Addiction is a chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

“Drug seeking” behavior is very common in addicts and drug abusers. 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, forging or counterfeiting prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” to obtain additional prescriptions is common among drug abusers, people suffering from untreated addiction and criminals seeking drugs to sell.

Physicians 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 addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Since DILAUDID INJECTION and DILAUDID-HP may be diverted for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

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

DILAUDID INJECTION and DILAUDID-HP are intended for parenteral use only under the direct supervision of an appropriately licensed health care provider. Misuse or abuse of DILAUDID INJECTION or DILAUDID-HP poses a risk of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

SAFETY AND HANDLING INSTRUCTIONS

DILAUDID INJECTION and DILAUDID-HP pose little risk of direct exposure to health care personnel and should be handled and disposed of prudently in accordance with hospital or institutional policy. Patients and their families should be instructed to flush any DILAUDID INJECTION or DILAUDID-HP that is no longer needed.

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

HOW SUPPLIED

DILAUDID INJECTION

DILAUDID INJECTION (hydromorphone hydrochloride) is available in CLEAR ampules. Each 1 mL of sterile aqueous solution contains 1 mg, 2 mg, or 4 mg hydromorphone hydrochloride with 0.2% sodium citrate and 0.2% citric acid solution. No added preservative. DILAUDID INJECTION ampules are sterile and are supplied as follows:

NDC 59011-441-10: Box of ten 1 mg/mL ampules

NDC 59011-442-10: Box of ten 2 mg/mL ampules

NDC 59011-442-25: Box of 25 2 mg/mL ampules

NDC 59011-444-10: Box of ten 4 mg/mL ampules

DILAUDID-HP

DILAUDID-HP (hydromorphone hydrochloride) is available in AMBER ampules and single dose vials. Each 1mL of sterile aqueous solution contains 10 mg hydromorphone hydrochloride with 0.2% sodium citrate and 0.2% citric acid solution. No added preservative.

DILAUDID-HP Sterile Lyophilized Powder contains 250 mg of sterile, lyophilized hydromorphone HCl in a Single Dose Vial. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

DILAUDID-HP ampules and single dose vials are sterile and are supplied as follows:

NDC 59011-445-01: Box of ten 1mL (10 mg) ampules

NDC 59011-445-05: Box of ten 5mL (50 mg) ampules

NDC 59011-445-50: One 50 mL (500 mg) Single-Dose Vial*

NDC 59011-446-25: One 250 mg single dose vial*

***The Packaging of These Products Contain Dry Natural Rubber**

Storage

PROTECT FROM LIGHT.

Keep covered in carton until time of use. Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

A Schedule **C-II** Narcotic. DEA Order Form Required.

Revised December, 22 2009

© 2010 Purdue Pharma L.P.

302211-0B

Manufactured by

Hospira, Inc., Lake Forest, IL 60045, U.S.A.

for

Purdue Pharma L.P. Stamford, CT 06901-3431

U.S. Patent Number 6,589,960