HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HYDROMORPHONE HYDROCHLORIDE INJECTION, USP safely and effectively. See full prescribing information for HYDROMORPHONE HYDROCHLORIDE INJECTION, USP.

HYDROMORPHONE HYDROCHLORIDE INJECTION, USP for intravenous, intramuscular and subcutaneous route CII

Initial U.S. Approval: 1984

WARNING: RISK OF RESPIRATORY DEPRESSION AND ABUSE

See full prescribing information for complete boxed warning

- **Hydromorphone hydrochloride is a Schedule II opioid agonist. Schedule II opioid agonists 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 outcome, including death.**

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

Hydromorphone hydrochloride is an opioid agonist indicated for the management of pain in patients where an opioid analgesic is appropriate. (1)

----------DOSAGE AND ADMINISTRATION----------

The usual starting dose is 1 mg to 2 mg *subcutaneously* or *intramuscularly* every 2 to 3 hours as necessary for pain. (2.3)

The usual starting dose for intravenous administration is 0.2 mg to 1 mg every 2 to 3 hours (2.4)

Patients with hepatic and renal impairment should be started on a lower starting dose. (2.5 & 2.6)

----------DOSAGE FORMS AND STRENGTHS----------

Hydromorphone Hydrochloride Injection, USP, 1 mg/mL, 2 mg/mL and 4 mg/mL is available in ampules, Carpuject™ and iSecure™ syringes and single dose vials for parenteral administration. (3)

----------CONTRAINDICATIONS----------

Hydromorphone hydrochloride is contraindicated in patients with:

- known hypersensitivity to hydromorphone (4),
- respiratory depression in the absence of resuscitative equipment (4),
- status asthmaticus (4)
- gastrointestinal obstruction, especially paralytic ileus (4).

----------WARNINGS AND PRECAUTIONS----------

Respiratory depression: increased risk in the elderly, debilitated patients, and those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction (5.1)

Abuse of hydromorphone hydrochloride poses a hazard of overdose and death (5.2)

Risk of medication errors: Hydromorphone does not convert to morphine on a milligram per milligram basis. Use Table 1 to convert. (5.3)

CNS effects: Alcohol, other opioids, CNS depressants, or illicit drugs may potentiate the central nervous system and respiratory depressant effects of hydromorphone. (5.4)

Infants born to mothers physically dependent on hydromorphone will also be physically dependent and may exhibit signs of withdrawal. (5.5)

Elevation of intracranial pressure: Respiratory depressant effects of hydromorphone promotes carbon dioxide retention that results in elevation of cerebrospinal fluid pressure, which can be markedly exaggerated in conditions predisposed to increased intracranial pressure. (5.6)

Hypotension: Hydromorphone may cause severe hypotension in those with a depleted blood volume or with concurrent administration of drugs such as phenothiazines or general anesthetics. Administer with caution to patients in circulatory shock. (5.7)

Use with caution in patients with biliary tract disease including pancreatitis (5.8)

Use with caution with a reduced initial dose in the elderly or debilitated and special risk patients. (5.9)

Use with caution in patients with alcoholism and other drug dependencies (5.10)

Use may impair mental and/or physical ability and can produce orthostatic hypotension (5.11)

----------ADVERSE REACTIONS----------

The most frequently observed adverse effects are light-headedness, dizziness, sedation, nausea, vomiting, sweating, flushing, dysphoria, euphoria, dry mouth, and pruritus.

Serious adverse reactions include respiratory depression and apnea, circulatory depression, respiratory arrest, shock and cardiac arrest. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Hospira, Inc. at 1-800-441-4100 or ProductComplaintsPP@hospira.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

CNS depressants: increased risk of respiratory depression, hypotension, profound sedation, or coma.

Mixed Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) may reduce the analgesic effect and/or precipitate withdrawal symptoms. (7.2)

MAO inhibitors: Allow at least 14 days after stopping MAOIs before initiating treatment with hydromorphone. (7.3)

Anticholinergics: Medications with anticholinergic activity when used with opioid analgesics may result in increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. (7.4)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Based on animal data, may cause fetal harm (8.1)

Labor and Delivery: Use with caution during labor (8.2)

Nursing mothers: Nursing should not be undertaken while a patient is receiving hydromorphone hydrochloride. (8.3)

Pediatrics: Safety and effectiveness in pediatric patients have not been established (8.4)

Geriatric patients: use with caution in elderly patients, initiate dose at low end of dosing range. (8.5)

Hepatic and Renal impairment: Start patients with hepatic and renal impairment on a lower starting dose (8.6, 8.7, 12.3)

Revised: 07/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: RISK OF RESPIRATORY DEPRESSION AND ABUSE

Hydromorphone Hydrochloride Injection, USP, is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid analgesics. Schedule II opioid agonists, including morphine, oxymorphone, hydromorphone, oxycodone, fentanyl and methadone, have the highest potential for abuse and risk of producing fatal overdose due to 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. (5.1)

Hydromorphone can be abused in a manner similar to other opioid agonists, legal or illicit. These risks should be considered when administering, prescribing, or dispensing Hydromorphone in situations where the healthcare professional is concerned about increased risk of misuse or abuse. (5.2)

1 INDICATIONS AND USAGE

Hydromorphone hydrochloride is indicated for the management of pain in patients where an opioid analgesic is appropriate.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Considerations

Selection of patients and administration of hydromorphone hydrochloride injection should be governed by the same principles that apply to the use of similar opioid analgesics to treat patients with acute or chronic pain, and depends upon a comprehensive assessment of the patient. Individualize treatment in every case, using non-opioid analgesics, opioids on an as needed basis and/or combination products, and chronic opioid therapy in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality, and the American Pain Society.

The nature of the pain, (severity, frequency, etiology, and pathophysiology) as well as the medical status of the patient, will affect selection of the starting dosage. Opioid analgesics, including hydromorphone hydrochloride injection, have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks.

2.2 Individualization of Dosage

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment. Give attention to the following:

- the age, general condition and medical status of the patient;
- the patient's degree of opioid tolerance;
- the daily dose, potency, and specific characteristics of the opioid the patient has been taking previously;
- concurrent medications;
- the type and severity of the patient's pain;
- risk factors for abuse or addiction; including whether the patient has a previous or current substance abuse problem, a family history of substance abuse, or a history of mental illness or depression;
- the balance between pain control and adverse reactions

Periodic reassessment after the initial dosing of hydromorphone hydrochloride injection is required. If pain management is not satisfactory, and opioid-induced adverse events are tolerable, the hydromorphone dose may be increased gradually. If excessive opioid side effects are observed early in the

dosing interval, reduce the hydromorphone hydrochloride dose. 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 and the occurrence of adverse events than the absolute dose of opioid employed.

2.3 Subcutaneous or Intramuscular Administration

The usual starting dose is 1 mg to 2 mg *subcutaneously* or *intramuscularly* every 2 to 3 hours as necessary for pain. Depending on the clinical situation, the initial starting dose may be lowered in patients who are opioid naïve. Adjust the dose according to the severity of pain and occurrence of adverse events, as well as the patient's underlying disease and age.

2.4 Intravenous Administration

The initial intravenous starting dose is 0.2 mg to 1 mg every 2 to 3 hours as necessary for pain control.

Administer intravenous hydromorphone **slowly**, over at least 2 to 3 minutes, depending on the dose. Titrate the dose to achieve acceptable pain management and tolerable adverse events. Reduce the initial dose in the elderly or debilitated.

2.5 Hepatic Impairment

Start patients with hepatic impairment on one-fourth to one-half the usual dose of hydromorphone hydrochloride injection depending on the extent of impairment [*see Clinical Pharmacology, Pharmacokinetics and Metabolism (12.3)*].

2.6 Renal Impairment

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

2.7 Conversion from Prior Opioid

Use the equianalgesic dose table below (Table 1) as a guide to determine the appropriate dose of hydromorphone injection. Convert the current total daily amount(s) of opioid(s) received to an equivalent total daily dose of hydromorphone injection and reduce by one-half due to the possibility of incomplete cross tolerance. Divide the new total amount by number of doses permitted based on dosing interval (e.g. 8 doses for every-three-hour dosing). Titrate the dose according to the patient's response. For opioids not in Table 1, first estimate the daily amount of morphine that is equivalent to the current total daily amount of other opioid(s) received, then use Table 1 to find the approximate equivalent total daily dose of hydromorphone injection.

Table 1 OPIOID ANALGESIC EQUIVALENTS WITH APPROXIMATELY EQUIANALGESIC POTENCY FOR CONVERSION TO HYDROMORPHONE INJECTION*

DRUG SUBSTANCE	PARENTERAL 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	10 – 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.

2.8 Administration

Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit. A slight yellowish discoloration may develop in hydromorphone hydrochloride ampules. No loss of potency has been demonstrated. Hydromorphone hydrochloride is physically compatible and chemically stable for at least 24 hours at 25°C protected from light in most common large volume parenteral solutions.

3 DOSAGE FORMS AND STRENGTHS

Hydromorphone hydrochloride injections are available as:

- Ampules 1 mg/mL, 2 mg/mL, and 4 mg/mL
- Carpuject Syringes 1 mg/mL, 2 mg/mL, and 4 mg/mL
- iSecure Syringes 0.5 mg/0.5 mL, 1 mg/mL, and 2 mg/mL
- Vials 2 mg/mL

The drug product is a clear, colorless to nearly colorless aqueous sterile solution. Each 1 mL of sterile solution contains 1 mg, 2 mg or 4 mg hydromorphone hydrochloride.

4 CONTRAINDICATIONS

Hydromorphone hydrochloride is contraindicated:

- in patients with known hypersensitivity to hydromorphone
- in any situation where opioids are contraindicated, e.g., in patients with respiratory depression in the absence of resuscitative equipment or in unmonitored settings; or patients with acute or severe bronchial asthma
- in patients with, or at risk of developing, gastrointestinal obstruction, especially paralytic ileus because hydromorphone diminishes the propulsive peristaltic wave in the gastrointestinal tract and may prolong the obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Respiratory Depression

Respiratory depression is the chief hazard of hydromorphone hydrochloride. 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. Respiratory depression is also a particular problem following large initial doses in non opioid-tolerant patients or when opioids are given in conjunction with other agents that depress respiration.

Use hydromorphone hydrochloride 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 hydromorphone hydrochloride should be employed only under careful medical supervision at the lowest effective dose in such patients.

5.2 Misuse and Abuse of Opioids

Hydromorphone is an opioid agonist with an abuse liability similar to morphine and a Schedule II, controlled substance. Hydromorphone has the potential for being abused, is sought by drug abusers and people with addiction disorders, and is subject to criminal diversion. Diversion of Schedule II products is an act subject to criminal penalty.

Abuse of hydromorphone hydrochloride poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol or other substances. Schedule II opioid agonists have the highest potential for abuse and risk of fatal respiratory depression.

Hydromorphone injection can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing hydromorphone injection in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

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.

5.3 Risk of Medication Errors

Hydromorphone for parenteral administration is marketed in several concentrations. Take precautions to ensure that the different concentrations are not confused to avoid the risk of accidental overdose and death.

Hydromorphone does not convert to morphine on a milligram per milligram basis. Use Table 1 when converting a patient from morphine to hydromorphone to avoid errors that can lead to overdose or death.

5.4 Interactions with Alcohol, CNS Depressants, and Drugs of Abuse

The concurrent use of hydromorphone hydrochloride with other central nervous system (CNS) depressants, including but not limited to other opioids, illicit drugs, sedatives, hypnotics, general anesthetics, phenothiazines, muscle relaxants, other tranquilizers, and alcohol, increases the risk of respiratory depression, hypotension, and profound sedation, potentially resulting in coma or death. Use with caution and in reduced dosages in patients taking CNS depressants.

5.5 Neonatal Withdrawal Syndrome

Infants born to mothers physically dependent on hydromorphone hydrochloride injection will also be physically dependent and may exhibit signs of withdrawal. 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. Neonatal opioid withdrawal syndrome may be life threatening and should be treated according to protocols developed by neonatology experts [*see Drug Abuse and Dependence (9.3)*].

5.6 Use in Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of hydromorphone hydrochloride injection promote carbon dioxide retention which results in elevation of cerebrospinal fluid pressure. This increase in intracranial pressure may be markedly exaggerated in the presence of head injury, intracranial lesions, or other conditions that predispose to increased intracranial pressure.

Hydromorphone hydrochloride injection 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.

5.7 Hypotensive Effects

Hydromorphone hydrochloride may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a depleted blood volume, or a concurrent administration of drugs such as phenothiazines or general anesthetics [*see Warnings and Precautions (5), Drug Interactions (7)*]. Hydromorphone hydrochloride may product orthostatic hypotension in ambulatory patients.

Administer hydromorphone hydrochloride with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

5.8 Use in Pancreatic/Biliary Tract Disease and Other Gastrointestinal Conditions

The administration of hydromorphone hydrochloride injection may obscure the diagnosis or clinical course in patients with acute abdominal conditions [*see Contraindications (4)*].

Use hydromorphone hydrochloride injection with caution in patients who are at risk of developing ileus.

Use hydromorphone hydrochloride injection 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.

5.9 Special Risk Patients

Give hydromorphone hydrochloride 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 associated with respiratory depression.

The administration of opioid analgesics including hydromorphone hydrochloride injection may aggravate preexisting convulsions in patients with convulsive disorders.

Hydromorphone, as with other opioids, may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings.

Reports of mild to severe seizures and myoclonus have been reported in severely compromised patients, administered high doses of parenteral hydromorphone.

5.10 Use in Drug and Alcohol Dependent Patients

Use hydromorphone hydrochloride 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 hydromorphone hydrochloride 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. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia.

5.11 Use in Ambulatory Patients

Hydromorphone hydrochloride may impair the mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients should be cautioned accordingly. Hydromorphone hydrochloride may produce orthostatic hypotension in ambulatory patients [*see Drug Interactions (7)*].

5.12 Parenteral Administration

Hydromorphone hydrochloride injection may be given intravenously, but the injection should be given very slowly. Rapid intravenous injection of opioid analgesics increases the possibility of side effects such as hypotension and respiratory depression [*see Dosage and Administration (2.3)*].

6 ADVERSE REACTIONS

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

Serious adverse reactions associated with hydromorphone hydrochloride include respiratory depression and apnea, and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest have occurred.

The following serious adverse reactions described elsewhere in the labeling include:

- Respiratory depression and secondary effects on intracranial pressure [*see Warnings and Precautions (5.1, 5.6)*].
- Hypotension [*see Warnings and Precautions (5.7)*].
- Gastrointestinal effects and effects in sphincter of Oddi [*see Warnings and Precautions (5.8)*].
- Drug abuse, addiction, and dependence [*see Drug Abuse and Dependence (9.2, 9.3)*].
- Effects on the ability to drive and operate machinery [*see Warnings and Precautions (5.11)*].

The most common adverse effects are light-headedness, 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.

6.1 Less Frequently Observed Adverse Reactions

Cardiac disorders: tachycardia, bradycardia, palpitations

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

Gastrointestinal disorders: constipation, ileus, diarrhea, abdominal pain

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

Hepatobiliary disorders: biliary colic

Metabolism and nutrition disorders: decreased appetite

Musculoskeletal and connective tissue disorders: muscle rigidity

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

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

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

Respiratory, thoracic and mediastinal disorders: bronchospasm, laryngospasm

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

Vascular disorders: flushing, hypotension, hypertension

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of hydromorphone. Because these events 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: anaphylactic reactions, confusional state, convulsions, dyskinesia, dyspnea, erectile dysfunction, hepatic enzyme increased, hyperalgesia, hypersensitivity reaction, injection site reactions, myoclonus, oropharyngeal swelling, peripheral edema, somnolence.

7 DRUG INTERACTIONS

7.1 Interactions with other CNS Depressants

Hydromorphone hydrochloride injection should be used with caution and in reduced dosages when administered to patients concurrently receiving other central nervous system depressants including

sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result.

When such combined therapy is contemplated, the dose of one or both agents should be reduced. Opioid analgesics, including hydromorphone hydrochloride, may enhance the action of neuromuscular blocking agents and produce an increased degree of respiratory depression.

7.2 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.

7.3 Monoamine Oxidase Inhibitors (MAOIs)

MAOIs may potentiate the action of hydromorphone hydrochloride. Allow at least 14 days after stopping treatment with MAOIs before initiating treatment with hydromorphone hydrochloride.

7.4 Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics including hydromorphone hydrochloride injection may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Hydromorphone crosses the placenta. Hydromorphone hydrochloride injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No effects on teratogenicity or embryotoxicity were observed in pregnant rats given oral doses up to 7 mg/kg/day which is 3-fold higher than the human dose of 24 mg hydromorphone hydrochloride injection (4 mg every 4 hours), on a body surface area basis. Hydromorphone administration to pregnant Syrian hamsters and CF-1 mice during major organ development revealed teratogenic effects likely the result of maternal toxicity associated with sedation and hypoxia. In Syrian hamsters given single subcutaneous doses from 14 to 258 mg/kg during organogenesis (gestation days 8-10), doses $\geq$ 19 mg/kg of hydromorphone produced skull malformations (exencephaly and cranioschisis). In CF-1 mice, continuous infusion of hydromorphone ($\geq$ 15 mg/kg over 24 hours) via implanted osmotic pumps during organogenesis (gestation days 7-10) produced soft tissue malformations (cryptorchidism, cleft palate, malformed ventricles and retina), and skeletal variations (split supraoccipital, checkerboard and split sternebrae, delayed ossification of the paws and ectopic ossification sites). The malformations and variations observed in the hamsters and mice were observed at doses approximately 6-fold and 3-fold higher, respectively, than the human dose of 24 mg hydromorphone hydrochloride (4 mg every 4 hours), on a body surface area basis.

8.2 Labor And Delivery

Hydromorphone hydrochloride should be used with caution during labor. Occasionally, opioid analgesics including hydromorphone hydrochloride injection may prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

Opioid analgesics, including hydromorphone hydrochloride, may cause respiratory depression in the newborn. Closely observe neonates whose mothers received opioid analgesics during labor for signs

of respiratory depression. Have a specific opioid antagonist, such as naloxone or nalmefene, available for reversal of opioid-induced respiratory depression in the neonate.

Neonates whose mothers have been taking opioids chronically may also exhibit withdrawal signs, either at birth or in the nursery, because they have developed physical dependence. This is not, however, synonymous with addiction [*see Drug Abuse and Dependence (9.3)*]. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and should be treated according to protocols developed by neonatology experts [*see Warnings and Precautions (5.5)*].

The effect of hydromorphone hydrochloride, if any, on the later growth, development, and functional maturation of the child is unknown.

8.3 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 hydromorphone hydrochloride injection since it, and other drugs in this class, may be excreted in the milk.

8.4 Pediatric Use

The safety and effectiveness of hydromorphone hydrochloride injection in pediatric patients has not been established.

8.5 Geriatric Use

Clinical studies of hydromorphone hydrochloride 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. Respiratory depression is the chief risk in elderly or debilitated patients, usually the result of large initial doses in non-opioid-tolerant patients. Titration in these patients should proceed cautiously [*see Individualization of Dosage (2.2) and Warnings and Precautions (5)*].

8.6 Renal Impairment

The pharmacokinetics of hydromorphone following an oral administration of hydromorphone at a single 4 mg dose (2 mg hydromorphone immediate-release tablets) are affected by renal impairment. Mean exposure to hydromorphone (C_{max} and $AUC_{0-\infty}$) 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). Start patients with renal impairment on one-fourth to one-half the usual starting dose depending on the degree of impairment. Patients with renal impairment should be closely monitored during dose titration. [*see Clinical Pharmacology (12.3)*]

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Hydromorphone hydrochloride injection is a Schedule II controlled substance with an abuse liability similar to morphine. Hydromorphone hydrochloride can be abused and is subject to criminal diversion.

9.2 Abuse

Hydromorphone hydrochloride injection is intended for parenteral use only under the direct supervision of an appropriately licensed health care professional.

Abuse of hydromorphone hydrochloride injection poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol or other substances. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Hydromorphone hydrochloride injection can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing, dispensing, ordering, or administering hydromorphone hydrochloride injection 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 indications of abuse.

Opioid drugs are sought by people with substance use disorders (abuse or addiction, the latter of which is also called “substance dependence”) and criminals who supply them by diverting medicines out of legitimate distribution channels. Hydromorphone hydrochloride injection is a target for diversion.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include, but are not limited to, emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, altering or forging of 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 people with untreated substance use disorders, and criminals who divert controlled substances.

The risks of misuse and abuse should be considered when prescribing or dispensing hydromorphone hydrochloride injection. Concerns about abuse and addiction, should not prevent the proper management of pain, however. Treatment of pain should be individualized, balancing the potential benefits and risks for each patient.

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.

Abuse and addiction are separate and distinct from physical dependence and tolerance. 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. 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, proper dispensing and correct storage and handling are appropriate measures that help to limit misuse and

abuse of opioid drugs. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

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.

9.3 Dependence

Tolerance to opioids is demonstrated by the need for increasing doses to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance to different effects of opioids may develop to varying degrees and at varying rates in a given individual. There is also inter-patient variability in the rate and extent of tolerance that develops to various opioid effects, whether the effect is desirable (e.g., analgesia) or undesirable (e.g., nausea). In general, patients taking opioid analgesics that are appropriately titrated for pain control develop tolerance to the respiratory depressant effects fairly reliably. Conversely, tolerance to the constipating effects of opioids rarely develops, even when they are administered over long periods of time.

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.

10 OVERDOSAGE

10.1 Signs and Symptoms

Signs and symptoms of acute overdosage with hydromorphone hydrochloride injection include: respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, apnea, circulatory collapse, cardiac arrest, and death.

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.

10.2 Treatment

In the treatment of overdosage, primary attention should be given to re-establishment of a patent airway and institution of assisted or controlled ventilation. 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.

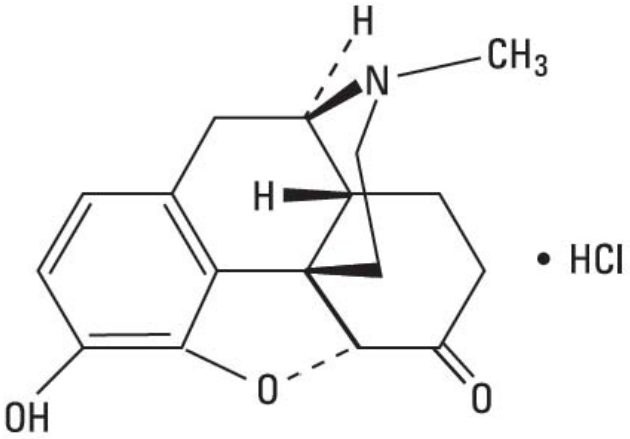
The opioid antagonists, naloxone, is a specific antidote against respiratory depression which may result from overdosage, or unusual sensitivity to hydromorphone hydrochloride. Therefore an appropriate dose of this antagonist should be administered preferably by the intravenous route, simultaneously 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 hydromorphone hydrochloride. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

Since the duration of action of hydromorphone hydrochloride 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.

11 DESCRIPTION

Hydromorphone hydrochloride, a hydrogenated ketone of morphine, is an opioid analgesic. The chemical name of hydromorphone hydrochloride is 4,5α- epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride.

The structural formula is:



The drug product is an aqueous sterile solution. Each 1 mL of sterile solution contains 1 mg, 2 mg, or 4 mg hydromorphone hydrochloride for the respective product strength. Each 1 mL also contains 5.4 mg sodium lactate and sodium chloride for isotonicity. The solution pH is adjusted with lactic acid or sodium hydroxide to between pH 3.5 and 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 hydrochloride is a mu-opioid receptor agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, fentanyl, codeine, hydrocodone and oxymorphone.

Central Nervous System

Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, and cough suppression, as well as analgesia.

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).

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.

Immune System

In vitro and animal studies indicate that opioids have a variety of effects on immune functions. The clinical significance of these findings is unknown.

12.3 Pharmacokinetics

Distribution

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

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 hydromorphone immediate-release tablets), mean exposure to hydromorphone (C_{max} and AUC_{∞}) is increased 4 fold in patients with moderate (Child-Pugh Group B) hepatic impairment compared with subjects with normal hepatic function. Patients with moderate hepatic impairment should be started at one fourth to one half the recommended starting dose and closely monitored during dose titration. The pharmacokinetics of hydromorphone in patients with severe hepatic impairment has not been studied. A further increase in C_{max} and AUC of hydromorphone in this group is expected and should be taken into consideration when selecting a starting dose [*see Use in Specific Populations (8.7)*].

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). Start patients with renal impairment on one-fourth to one-half the usual starting dose depending on the degree

of impairment. Patients with renal impairment should be closely monitored during dose titration [*see Use in Specific Populations (8.6)*].

Pediatrics

Pharmacokinetics of hydromorphone have not been evaluated in children.

Geriatric

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

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.

Race

The effect of race on hydromorphone pharmacokinetics has not been studied.

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

Hydromorphone was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames assay). Hydromorphone was not clastogenic in either the *in vitro* human lymphocyte chromosome aberration assay or the *in vivo* mouse micronucleus assay.

Impairment of Fertility

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 3-fold higher than the human dose of 24 mg hydromorphone hydrochloride injection (4 mg every 4 hours), on a body surface area basis.

14 CLINICAL STUDIES

Analgesic effects of single doses of hydromorphone hydrochloride 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 hydromorphone hydrochloride oral liquid provided significantly more analgesia than placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Safety and Handling Instructions

Hydromorphone hydrochloride injection poses little risk of direct exposure to health care personnel and should be handled and disposed of prudently in accordance with hospital or institutional policy. When hydromorphone hydrochloride injection is no longer needed, any unused liquid should be destroyed by flushing it down the toilet.

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

16.2 How Supplied

Ampul, Box of 10, 1 mL (1 mg/mL); NDC 0409-2552-01

Ampul, Box of 10, 1 mL (2 mg/mL); NDC 0409-3356-01

Ampul, Box of 10, 1 mL (4 mg/mL); NDC 0409-2540-01

Carpuject™, Single-dose cartridge with Luer Lock for the Carpuject Syringe System, Box of 10, 1 mL (1 mg/mL); NDC 0409-1283-31

Carpuject™, Single-dose cartridge with Luer Lock for the Carpuject Syringe System, Box of 10, 1 mL (2 mg/mL); NDC 0409-1312-30

Carpuject™ Single-dose cartridge with Luer Lock for the Carpuject Syringe System, Box of 10, 1 mL (4 mg/mL); NDC 0409-1304-31

iSecure Single-dose Prefilled Syringe with Luer Lock, Box of 10, 0.5 mL (1 mg/mL); NDC 0409-1283-05

iSecure Single-dose Prefilled Syringe with Luer Lock, Box of 10, 1 mL (1 mg/mL); NDC 0409-1283-10

iSecure Single-dose Prefilled Syringe with Luer Lock, Box of 10, 1 mL (2 mg/mL); NDC 0409-1312-10

Single Dose Vial, Tray of 25, 1 mL (2 mg/mL); NDC 0409-3365-01

16.3 Storage

PROTECT FROM LIGHT

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

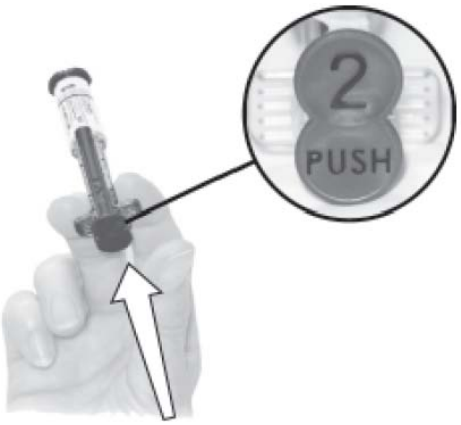
16.4 Instructions for Use of the Syringe Systems

Instructions for using the Carpuject Syringe are available with the reusable Carpuject Holder, List 2049-02.

To Use iSecure™ Syringe

1. Remove green tamper evident band in a clockwise motion.

2. Depress (Push) the plunger rod. This will loosen the plunger rod that is located on the outside of the syringe barrel so that the plunger rod can be removed. This will also engage the syringe.



Remove the plunger rod.

Insert the plunger rod into the back end of the syringe barrel and turn clockwise 2 to 3 times to attach.

BEFORE REMOVING LUER TIP CAP, hold the syringe with tip cap upright. Press syringe plunger until plunger moves slightly. This motion breaks the seal between plunger and syringe barrel.

3. Twist the luer tip cap clockwise or counterclockwise to break the tamper evident label. Remove the luer tip cap and discard it.

   Expel the air by pushing on the plunger rod.

   Attach needle or blunt cannula if required.

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