

opioids in certain susceptible populations. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

5.16 Increased Risk of Hypotension and Respiratory Depression with Rapid Intravenous Administration
Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] may be given intravenously, but this injection should be given very slowly. Rapid intravenous injection of opioid analgesics increases the possibility of side effects such as hypotension and respiratory depression [see Dosage and Administration (2)].

6 ADVERSE REACTIONS
The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse [see Warnings and Precautions (5.2)]
- Life-Threatening Respiratory Depression [see Warnings and Precautions (5.3)]
- Interactions with Benzodiazepines and Other CNS Depressants [see Warnings and Precautions (5.4)]
- Neonatal Opioid Withdrawal Syndrome [see Warnings and Precautions (5.5)]
- Opioid-Induced Hyperalgesia and Allodynia [see Warnings and Precautions (5.6)]
- Adrenal Insufficiency [see Warnings and Precautions (5.8)]
- Severe Hypotension [see Warnings and Precautions (5.9)]
- Gastrointestinal Adverse Reactions [see Warnings and Precautions (5.11)]
- Seizures [see Warnings and Precautions (5.12)]
- Withdrawal [see Warnings and Precautions (5.13)]

The following adverse reactions associated with the use of hydromorphone were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serious adverse reactions associated with Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] include respiratory depression and apnea and, to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest.

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

Less Frequently Observed Adverse Reactions
Cardiac disorders: tachycardia, bradycardia, palpitations
Eye disorders: vision blurred, diplopia, miosis, visual impairment
Gastrointestinal disorders: constipation, ileus, diarrhea, abdominal pain
General disorders and administration site conditions: weakness, feeling abnormal, chills, injection site urticaria, fatigue, injection site reactions, peripheral edema
Hepatobiliary disorders: biliary colic
Immune system disorders: anaphylactic reactions, hypersensitivity reactions
Investigations: hepatic enzymes increased
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, convulsion, drowsiness, dyskinesia, hyperalgesia, lethargy, myoclonus, somnolence
Psychiatric disorders: agitation, mood altered, nervousness, anxiety, depression, hallucination, disorientation, insomnia, abnormal dreams
Renal and urinary disorders: urinary retention, urinary hesitancy, antidiuretic effects
Reproductive system and breast disorders: erectile dysfunction
Respiratory, thoracic, and mediastinal disorders: bronchospasm, laryngospasm, dyspnea, oropharyngeal swelling
Skin and subcutaneous tissue disorders: injection site pain, urticaria, rash, hyperhidrosis
Vascular disorders: flushing, hypotension, hypertension
Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.
Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
Anaphylaxis: Anaphylaxis has been reported with ingredients contained in Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)].
Androgen deficiency: Cases of androgen deficiency have occurred with use of opioids for an extended period of time [see Clinical Pharmacology (12.2)].
Hyperalgesia and Allodynia: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration [see Warnings and Precautions (5.6)].
Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).

DRUG INTERACTIONS
Table 1 includes clinically significant drug interactions with Hydromorphone Hydrochloride Injection and/or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)].

TABLE 1. Clinically Significant Drug Interactions with Hydromorphone Hydrochloride Injection and/or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)]

Drug Class	Interaction
Benzodiazepines and other Central Nervous System Depressants (CNS)	Due to additive pharmacologic effect, the concomitant use of benzodiazepines and other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death. [see Warnings and Precautions (5.4)]
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Monitor patients closely for signs of respiratory depression and sedation [see Warnings and Precautions (5.4)].
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.

TABLE 1. Clinically Significant Drug Interactions with Hydromorphone Hydrochloride Injection and/or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)]

TABLE 1. Clinically Significant Drug Interactions with Hydromorphone Hydrochloride Injection and/or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] (Continued)

Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see Warnings and Precautions (5.3)]. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.
Intervention:	The use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) is not recommended for patients taking MAOIs or within 14 days of stopping such treatment. If urgent use of an opioid is necessary, use test doses and frequent titration of small doses while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.
Examples:	phenazine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) and/or precipitate withdrawal syndrome.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Hydromorphone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) are used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Use of opioid analgesics for an extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome [see Warnings and Precautions (5.5)]. There are no available data with Hydromorphone Hydrochloride Injection in pregnant women to inform a drug-associated risk for major birth defects and miscarriage or adverse maternal outcomes. There are adverse outcomes reported with fetal exposure to opioid analgesics [see Clinical Considerations].

In animal reproduction studies, reduced postnatal survival of pups, and decreased body weight were noted following oral treatment of pregnant rats with hydromorphone during gestation and through lactation at doses of 0.8 times the human daily dose of 24 mg/day (HDD), respectively. In published studies, neural tube defects were noted following subcutaneous injection of hydromorphone to pregnant hamsters at doses 6.4 times the HDD and soft tissue and skeletal abnormalities were noted following subcutaneous continuous infusion of 3 times the HDD to pregnant mice. No malformations were noted at 4 or 40 times the HDD in pregnant rats or rabbits, respectively [see Data]. Based on animal data, advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Use of opioid analgesics for an extended period of time during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [see Warnings and Precautions (5.5)].

Labor or Delivery
Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF), can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data

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

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

In a published study, neural tube defects (exencephaly and cranioschisis) were noted following subcutaneous administration of hydromorphone hydrochloride (19 to 258 mg/kg) on Gestation Day 8 to pregnant hamsters (6.4 to 87.2 times the HDD of 24 mg/day based on body surface area). The findings cannot be clearly attributed to maternal toxicity. No neural tube defects were noted at 14 mg/kg (4.7 times the human daily dose of 24 mg/day).

In a published study, CF-1 mice were treated subcutaneously with continuous infusion of 7.5, 15, or 30 mg/kg/day hydromorphone hydrochloride (1.5, 3, or 6.1 times the human daily dose of 24 mg based on body surface area) via implanted osmotic pumps during organogenesis (Gestation Days 7 to 10).

Soft tissue malformations (cryptorchidism, cleft palate, malformed ventricles and retina), and skeletal variations (split supracapital, checkerboard and split sternbrae, delayed ossification of the paws and ectopic ossification sites) were observed at doses 3 times the human dose of 24 mg/day based on body surface area. The findings cannot be clearly attributed to maternal toxicity.

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

8.2 Lactation

Risk Summary

Low levels of opioid analgesics have been detected in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] and any potential adverse effects on the breastfed infant from Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of hydromorphone is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Use of opioids for an extended period of time may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Adverse Reactions (6), Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

The safety and effectiveness of Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] in pediatric patients has not been established.

8.5 Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to hydromorphone and caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see Warnings and Precautions (5.7)].

Hydromorphone is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

The pharmacokinetics of hydromorphone are affected by hepatic impairment. Due to increased exposure of hydromorphone, patients with moderate hepatic impairment should be started at one-fourth to

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

8.7 Renal Impairment

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

9 DRUG ABUSE AND DEPENDENCE

Controlled Substance

Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] contain hydromorphone, which is a Schedule II controlled substance.

9.2 Abuse

Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] contains hydromorphone, a substance with high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction [see Warnings and Precautions (5.2)].

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] with alcohol and/or other CNS depressants. Abuse of and addition to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] abuse include those with a history of prolonged use of any opioid, including products containing hydromorphone, those with a history of drug or alcohol abuse, or those who use Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] in combination with other abused drugs.

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

Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)], like other opioids, can be diverted for nonmedical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

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

Risks Specific to Abuse of Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)]

Abuse of Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) poses a risk of overdose and death. The risk is increased with concurrent use of Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) with alcohol and/or other CNS depressants.

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

9.3 Dependence

Both tolerance and physical dependence can develop during use of opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur in a clinically significant degree until after several days to weeks of continued use.

Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] should not be abruptly discontinued in a physically-dependent patient [see Dosage and Administration (2.6)]. If Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency

formulation (HPF)] is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur, typically characterized by restlessness, lacrimation, rhinorrhea, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see Use in Specific Populations (8.1)].

10 OVERDOSAGE

Clinical Presentation

Acute overdose with hydromorphone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, hypoglycemia, partial or complete urinary obstruction, atypical snoring, and death. Marked mydriasis, rather than miosis, may be seen with hypoxia in overdose situations [see Clinical Pharmacology (12.2)].

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent airway and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support measures.

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

Because the duration of opioid reversal is expected to be less than the duration of hydromorphone in Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF), carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

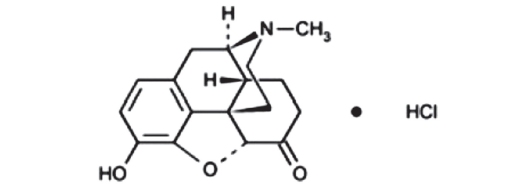
11 DESCRIPTION

Hydromorphone Hydrochloride, a hydrogenated ketone of morphine, is an opioid agonist.

Hydromorphone Hydrochloride Injection is available as a sterile, aqueous solution in single dose amber vials for slow intravenous, subcutaneous, or intramuscular administration. Each mL contains 1 mg, 2 mg, or 4 mg of hydromorphone hydrochloride with 0.2% sodium citrate and 0.2% citric acid added as a buffer to maintain a pH of between 3.5 and 5.5.

Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] is available as a sterile, aqueous solution in single dose amber vials for intravenous, subcutaneous, or intramuscular administration. Each single dose vial contains 10 mg/mL of hydromorphone hydrochloride with 0.2% sodium citrate and 0.2% citric acid added as a buffer to maintain a pH of between 3.5 and 5.5.

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



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

The inactive ingredients in Hydromorphone Hydrochloride Injection include 0.2% sodium citrate and 0.2% citric acid added as a buffer to maintain a pH between 3.5 and 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

Effects on the Central Nervous System

Hydromorphone produces respiratory depression by direct effect on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers. Beyond a certain point, care should be taken to avoid hypoxia, as both increases in carbon dioxide tension and electrical stimulation.

Hydromorphone causes miosis, even in total darkness. Pinpoint pupils are a sign of overdose when the pupils do not respond to 1 mg of 1% hydrochloride injection (1 mg/mL) of the parasympatholytic agent, atropine. In the presence of pupillary lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

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

Effects on the Cardiovascular System

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

Effects on the Endocrine System

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

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

Effects on the Immune System

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

Concentration-Efficacy Relationships

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

Concentration-Adverse Reaction Relationships

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

12.3 Pharmacokinetics

Distribution

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

Elimination

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

Metabolism

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

Excretion

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

Special Populations

Hepatic Impairment

After oral administration of hydromorphone at a single 4 mg dose (2 mg hydromorphone immediate-release tablets), mean exposure to hydromorphone (C_{max} and AUC_{0-∞}) 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