

HIGHLIGHTS OF PRESCRIBING INFORMATION		
These highlights do not include all the information needed to use HYDROMORPHONE HYDROCHLORIDE INJECTION and HYDROMORPHONE HYDROCHLORIDE INJECTION (HPF) safely and effectively.		
See full prescribing information for HYDROMORPHONE HYDROCHLORIDE INJECTION and HYDROMORPHONE HYDROCHLORIDE INJECTION (HPF). HYDROMORPHONE HYDROCHLORIDE injection and HYDROMORPHONE		
HYDROCHLORIDE injection [high potency formulation (HPF)], for intravenous, intramuscular, or subcutaneous use, CII		
Initial U.S. Approval: January 1984	Rx Only	
WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF HYDROMORPHONE HYDROCHLORIDE INJECTION AND HYDROMORPHONE HYDROCHLORIDE INJECTION (HPF) See full prescribing information for complete boxed warning. Do not confuse Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] with standard parenteral formulations of Hydromorphone Hydrochloride Injection or other opioids, as overdose and death could result. (5.1) Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient’s risk before prescribing and reassess regularly for these behaviors and conditions. (5.2) Serious, life-threatening, or fatal respiratory depression may occur, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) are essential. (5.3) Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate. (5.4, 7) Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery. (5.5)		
RECENT MAJOR CHANGES		
Boxed Warning	12/2025	
Indications and Usage (1)	12/2025	
Dosage and Administration (2.6)	12/2025	
Warnings and Precautions (5.2, 5.3, 5.4, 5.11, 5.13)	12/2025	
INDICATIONS AND USAGE		
Hydromorphone Hydrochloride Injection is an opioid agonist indicated for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate. (1)		
Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] is an opioid agonist indicated for use in opioid-tolerant patients who require higher doses of opioids for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate.		
Patients considered opioid tolerant are those who are taking, for one week or longer, around-the-clock medicine consisting of at least 60 mg of oral morphine per day, at least 25 mcg/hr of transdermal fentanyl per hour, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day, at least 25 mg oral oxymorphone per day, at least 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid daily for a week or longer. Patients must remain on around-the-clock opioids when administering Hydromorphone Hydrochloride Injection (HPF).		
Limitations of Use:		
• Because of the risks of addiction, abuse, misuse, overdose, and death, which can occur at any dosage or duration and persist over the course of therapy, reserve opioid analgesics, including Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)], for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1, 5.2)		
DOSAGE AND ADMINISTRATION		
• Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks. (2.1)		
• Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals. Reserve titration to higher doses of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks. (2.1, 5)		
• Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available. (2.1)		
• Initiate the dosing regimen for each patient individually, taking into account the patient’s underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse. (2.1, 5.2)		
FULL PRESCRIBING INFORMATION: CONTENTS*		
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WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF HYDROMORPHONE HYDROCHLORIDE INJECTION AND HYDROMORPHONE HYDROCHLORIDE INJECTION (HPF)

Risk of Medication Errors
Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] is a more concentrated solution of hydromorphone than Hydromorphone Hydrochloride Injection, and is for use in opioid-tolerant patients only. Do not confuse Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] with standard parenteral formulations of Hydromorphone Hydrochloride Injection or other opioids, as overdose and death could result [see Warnings and Precautions (5.1)].

Addiction, Abuse, and Misuse
Because the use of Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death, assess each patient’s risk prior to prescribing and reassess all patients regularly for the development of these behaviors and conditions [see Warnings and Precautions (5.2)].

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)], especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] are essential [see Warnings and Precautions (5.3)].

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate [see Warnings and Precautions (5.4), Drug Interactions (7)].

Neonatal Opioid Withdrawal Syndrome (NODS)
Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery [see Warnings and Precautions (5.5)].

1 INDICATIONS AND USAGE

Hydromorphone Hydrochloride Injection is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] is indicated for use in opioid-tolerant patients who require higher doses of opioids for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate.

Patients considered opioid tolerant are those who are taking for one week or longer, around-the-clock medicine consisting of at least 60 mg oral morphine per day, or at least 25 mcg transdermal fentanyl per hour, or at least 30 mg oral oxycodone per day, or at least 8 g oral hydromorphone per day, or at least 25 mg oral oxymorphone per day, or at least 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid for one week or longer. Patients must remain on around-the-clock opioids while administering Hydromorphone Hydrochloride Injection (HPF).

Limitations of Use:
Because of the risks of addiction, abuse, misuse, overdose, and death, which can occur at any dosage or duration and persist over the course of therapy [see Warnings and Precautions (5.3)], reserve opioid analgesics, including Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2026

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

- 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 Injection and Hydromorphone Hydrochloride Injection (HPF) vials. No loss of potency has been demonstrated. Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) are physically compatible and chemically stable for at least 24 hours at 25°C, protected from light in most common large-volume parenteral solutions.
- Discard any unused portion in an appropriate manner.

500 mg/50 mL Vial
To use this single dose presentation, withdraw the contents using aseptic technique for preparation of a single, large-volume parenteral solution. Discard any unused portion in an appropriate manner.

2.2 Initial Dosage

Use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] as the First Opioid Analgesic
Hydromorphone Hydrochloride Injection (HPF) is for use in opioid tolerant patients only. Do not use Hydromorphone Hydrochloride Injection (HPF) for patients who are not tolerant to the respiratory depressant or sedating effects of opioids.

Subcutaneous or Intramuscular Administration:
The usual starting dose is 1 mg to 2 mg every 2 to 3 hours as necessary for pain, and the lowest dose necessary to achieve adequate analgesia. Depending on the clinical situation, the initial starting dose may be lowered in patients who are opioid naïve. Titrate the dose based upon the individual patient’s response to their initial dose of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF).

Intravenous Administration:
The initial starting dose is 0.2 mg to 1 mg every 2 to 3 hours. Intravenous administration should be given slowly, over at least 2 to 3 minutes, depending on the dose. The initial dose should be reduced in the elderly or debilitated and may be lowered to 0.2 mg.

Conversion From Other Opioids to Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)]:

There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF). It is safer to underestimate a patient’s 24-hour Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) dosage than to overestimate the 24-hour Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) dosage and manage an adverse reaction due to overdose.

If the decision is made to convert to Hydromorphone Hydrochloride Injection from another opioid analgesic using publicly available data, convert the current total daily amount(s) of opioid(s) received to an equivalent total daily dose of Hydromorphone Hydrochloride Injection and reduce by one-half due to the possibility of incomplete cross tolerance. Divide the new total amount by the 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.

Assess each patient’s risk for opioid addiction, abuse, or misuse prior to prescribing Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF), and monitor all patients receiving Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF), but use in such patients necessitates intensive counseling about the risks and proper use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use.

Consider these risks when prescribing or dispensing Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF). Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Base the starting dose for Hydromorphone Hydrochloride Injection (HPF) on the prior dose of Hydromorphone Hydrochloride Injection or on the prior dose of an alternate opioid.

2.3 Dosage Modifications in Patients with Hepatic Impairment

Start patients with hepatic impairment on one-fourth to one-half the usual Hydromorphone Hydrochloride Injection starting dose depending on the extent of impairment [see Clinical Pharmacology (12.3)].

2.4 Dosage Modifications in Patients with Renal Impairment

Start patients with renal impairment on one-fourth to one-half the usual Hydromorphone Hydrochloride Injection starting dose depending on the degree of impairment [see Clinical Pharmacology (12.3)].

2.5 Titration and Maintenance of Therapy

Titrate the dose based upon the individual patient’s response to their initial dose of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF). Individually titrate Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and other adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [see Warnings and Precautions (5.2, 5.13)]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) dosage. If after increasing the dosage, unacceptable opioid-related adverse reactions are observed (including an increase in pain after a dosage increase), consider reducing the dosage [see Warnings and Precautions (5)]. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.6 Safe Reduction or Discontinuation of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF)

When a patient who has been taking Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] regularly and may be physically dependent no longer requires therapy with Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF), taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not rapidly reduce or abruptly discontinue Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) in patients who may be physically dependent on opioids. [see Warnings and Precautions (5.13), Drug Abuse and Dependence (9.3)].

3 DOSAGE FORMS AND STRENGTHS

Hydromorphone Hydrochloride Injection: Each 1 mL colorless single dose vial contains 1 mg/mL, 2 mg/mL, or 4 mg/mL of hydromorphone hydrochloride in a sterile, aqueous solution. Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] (for use in opioid-tolerant patients only):

Each amber single dose vial contains 10 mg/mL of hydromorphone hydrochloride in a sterile, aqueous solution and is available in 1 mL, 5 mL and 50 mL single dose vials.

4 CONTRAINDICATIONS

- Both Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] are contraindicated in patients with:
 - Significant respiratory depression [see Warnings and Precautions (5.3)]
 - Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see Warnings and Precautions (5.7)]
 - Known or suspected gastrointestinal obstruction, including paralytic ileus [see Warnings and Precautions (5.11)]
 - Hypersensitivity to hydromorphone, hydromorphone salts, any other components of the product, or sulfate containing medications (e.g., anaphylaxis) [see Warnings and Precautions (5.15)]

Hydromorphone Hydrochloride Injection (HPF) is contraindicated in patients who are not opioid tolerant [see Warnings and Precautions (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Medication Errors

Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] is a 10 mg/mL concentrated solution of hydromorphone, and is intended for use in opioid-tolerant patients only. Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

Do not confuse Hydromorphone Hydrochloride Injection (HPF) with standard parenteral formulations of Hydromorphone Hydrochloride Injection (1 mg/mL, 2 mg/mL, 4 mg/mL) or other opioids, as overdose and death could result.

5.2 Addition, Abuse, and Misuse

Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] contain hydromorphone, a Schedule II controlled substance. As an opioid, Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) exposes users to the risks of addiction, abuse, and misuse [see Drug Abuse and Dependence (9)].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF). Addiction can occur at recommended dosages and if the drug is misused or abused. The risk of opioid-related overdose or overdose-related death is increased with higher opioid doses, and this risk persists over the course of therapy. In postmarketing studies, addiction, abuse, misuse, and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use [see Adverse Reactions (6.2)].

Assess each patient’s risk for opioid addiction, abuse, or misuse prior to prescribing Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF), and monitor all patients receiving Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF), but use in such patients necessitates intensive counseling about the risks and proper use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use.

Consider these risks when prescribing or dispensing Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF). Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.3 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid overdose reversal agents (e.g., naloxone, nalbuphine), depending on the patient’s clinical status [see Overdosage (10)]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)], the risk is greatest during the initiation of therapy or following a dosage increase.

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

Hydromorphone Hydrochloride Injection (HPF) is for use in opioid-tolerant patients only. Administration of this formulation may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoventilation. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper [see Dosage and Administration (2.6)].

5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] with benzodiazepines and/or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin], and other opioids). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see Drug Interactions (7)].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Monitor patients closely for signs and symptoms of respiratory depression and sedation.

5.5 Neonatal Opioid Withdrawal Syndrome

Use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] for an extended period of time during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that management by neonatology experts will be available at delivery [see Use in Specific Populations (8.1)].

5.6 Opioid-Induced Hyperalgesia and Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect [see Dependence (9.3)]. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or additive behavior.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation (safely switching the patient to a different opioid moiety) [see Dosage and Administration (2.6), Warnings and Precautions (5.13)].

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

The use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease:
Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) [see Warnings and Precautions (5.3)].

Elderly, Cachectic, or Debilitated Patients:
Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see Warnings and Precautions (5.3)].

Monitor such patients closely, particularly when initiating and titrating Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] and when Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) are given concomitantly with other drugs that depress respiration [see Warnings and Precautions (5.3, 5.4), Drug Interactions (7)]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.8 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.9 Severe Hypotension

Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) [see Drug Interactions (7)]. Monitor these patients for signs of hypotension after initiating or titrating the dosage

of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF). In patients with circulatory shock, Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) may cause vasodilation that can further reduce cardiac output and blood

TABLE 1. Clinically Significant Drug Interactions with Hydromorphone Hydrochloride Injection and/or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] (Continued)	
Serotonergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
<i>Intervention:</i>	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) if serotonin syndrome is suspected.
<i>Examples:</i>	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)	
<i>Clinical Impact:</i>	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see <i>Warnings and Precautions</i> (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.
<i>Intervention:</i>	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.
<i>Examples:</i>	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
<i>Clinical Impact:</i>	May reduce the analgesic effect of Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) and/or precipitate withdrawal syndrome.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
<i>Clinical Impact:</i>	Hydromorphone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) and/or the muscle relaxant as necessary.
<i>Examples:</i>	cyclobenzaprine, metaxalone
Diuretics	
<i>Clinical Impact:</i>	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
<i>Intervention:</i>	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
<i>Intervention:</i>	Monitor patients for signs of urinary retention or reduced gastric motility when 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 <i>Warnings and Precautions</i> (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 <i>Clinical Considerations</i>].
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 0.8 times the human daily dose of 24 mg/day (HDD), respectively. In published studies, neural tube defects were noted following subcutaneous injection of hydromorphone to pregnant hamsters at doses 6.4 times the HDD and soft tissue and skeletal abnormalities were noted following subcutaneous continuous infusion of 3 times the HDD to pregnant mice. No malformations were noted at 4 or 40.5 times the HDD in pregnant rats or rabbits, respectively [see <i>Data</i>]. 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 <i>Warnings and Precautions</i> (5.5)].
Labor or Delivery
Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid overdose reversal agent, such as naloxone or nalmeftene, must be available for reversal of opioid-induced

A retrospective, observational cohort study estimated the risk of opioid-involved overdose or opioid overdose-related death in patients with new long-term use of Schedule II opioid analgesics from 2006 through 2016 (n=220,249). Included patients had been enrolled in either one of two commercial insurance programs, one managed care program, or one Medicaid program for at least 9 months. *New long-term use* was defined as having Schedule II opioid analgesic prescriptions covering at least 70 days' supply over the 3 months prior to study entry and none during the preceding 6 months. Patients were excluded if they had an opioid-involved overdose in the 9 months prior to study entry. Overdose was measured using a validated medical code-based algorithm with linkage to the National Death Index database. The 5-year cumulative incidence estimates for opioid-involved overdose or opioid overdose-related death ranged from approximately 1.5% to 4% across study sites, counting only the first event during follow-up. Approximately 17% of first opioid overdoses observed over the entire study period (5-11 years, depending on the study site) were fatal. Higher baseline opioid dose was the strongest and most consistent predictor of opioid-involved overdose or opioid overdose-related death. Study exclusion criteria may have selected patients at lower risk of overdose, and substantial loss to follow-up (approximately 80%) also may have biased estimates.

The risk estimates from the studies described above may not be generalizable to all patients receiving opioid analgesics, such as those with exposures shorter or longer than the duration evaluated in the studies.

7 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)]	
Benzodiazepines and other Central Nervous System Depressants (CNS)	
<i>Clinical Impact:</i>	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 <i>Warnings and Precautions</i> (5.4)]
<i>Intervention:</i>	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Monitor patients closely for signs of respiratory depression and sedation [see <i>Warnings and Precautions</i> (5.4)].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antiepileptics, gabapentinoids (gabapentin or pregabalin), other opioids, alcohol.

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. Gastrointestinal disorders: constipation, ileus, biliary colic, 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 hesitation, 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). *Opioid-induced esophageal dysfunction (OIED):* Cases of OIED have been reported in patients taking opioids and may occur more frequently in patients taking higher doses of opioids, and/or in patients taking opioids longer term [see *Warnings and Precautions* (5.11)].

Adverse Reactions from Observational Studies
A prospective, observational cohort study estimated the risks of addiction, abuse, and misuse in patients initiating long-term use of Schedule II opioid analgesics between 2017 and 2021. Study participants included in one or more analyses had been enrolled in selected insurance plans or health systems for at least one year, were free of at least one outcome at baseline, completed a minimum number of follow-up assessments, and either: 1) filled multiple extended-release/long-acting opioid analgesic prescriptions during a 90-day period (n=978); or 2) filled any Schedule II opioid analgesic prescriptions covering at least 70 of 90 days (n=1,244). Those included also had no dispensing of the qualifying opioids in the previous 6 months.

Over 12 months:
• approximately 1% to 6% of participants across the two cohorts newly met criteria for addiction, as assessed with two validated interview-based measures of moderate-to-severe opioid use disorder based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, and
• approximately 9% and 22% of participants across the two cohorts newly met criteria for prescription opioid abuse and misuse [defined in *Drug Abuse and Dependence* (9.2)], respectively, as measured with a validated self-reported instrument.

A retrospective, observational cohort study estimated the risk of opioid-involved overdose or opioid overdose-related death in patients with new long-term use of Schedule II opioid analgesics from 2006 through 2016 (n=220,249). Included patients had been enrolled in either one of two commercial insurance programs, one managed care program, or one Medicaid program for at least 9 months. *New long-term use* was defined as having Schedule II opioid analgesic prescriptions covering at least 70 days' supply over the 3 months prior to study entry and none during the preceding 6 months. Patients were excluded if they had an opioid-involved overdose in the 9 months prior to study entry. Overdose was measured using a validated medical code-based algorithm with linkage to the National Death Index database. The 5-year cumulative incidence estimates for opioid-involved overdose or opioid overdose-related death ranged from approximately 1.5% to 4% across study sites, counting only the first event during follow-up. Approximately 17% of first opioid overdoses observed over the entire study period (5-11 years, depending on the study site) were fatal. Higher baseline opioid dose was the strongest and most consistent predictor of opioid-involved overdose or opioid overdose-related death. Study exclusion criteria may have selected patients at lower risk of overdose, and substantial loss to follow-up (approximately 80%) also may have biased estimates.

The risk estimates from the studies described above may not be generalizable to all patients receiving opioid analgesics, such as those with exposures shorter or longer than the duration evaluated in the studies.

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. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of 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

9.1 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 addiction 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)] 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.

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

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

In a published study, C57-BL/6J 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).

“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. Precontemplation 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.

Parental 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, nalmeftene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued use.

Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] should not be rapidly reduced or 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 rapidly reduced or 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 airway obstruction, atypical snoring, and death. Marked mydriasis, rather than miosis, may be seen with hypoxia in overdose situations [see *Clinical Pharmacology* (12.2)]. Toxic leukoencephalopathy has been reported after opioid overdose and can present hours, days, or weeks after apparent recovery from the initial intoxication.

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.

For clinically significant respiratory or circulatory depression secondary to hydromorphone overdose, administer an opioid overdose reversal agent such as naloxone or nalmeftene.

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 overdose reversal agent is suboptimal or only brief in nature, administer additional reversal agent as directed by the product's prescribing information.

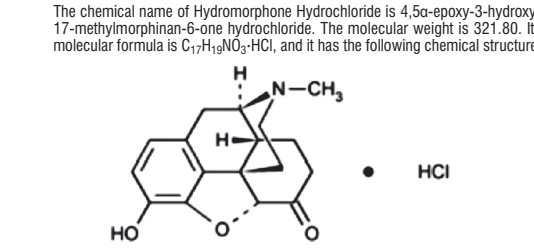
In an individual physically dependent on opioids, administration of the recommended usual dosage of the opioid overdose reversal agent will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the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

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

Hydromorphone Hydrochloride Injection is available as a sterile, aqueous solution in single dose colorless 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 4,5o-epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride. The molecular weight is 321.80. Its molecular formula is $C_{17}H_{19}NO_3 \cdot HCl$, 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 to both increases in carbon dioxide tension and electrical stimulation.

Hydromorphone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic 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 reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, transient elevations in serum amylase, and opioid-induced esophageal dysfunction (OIED).

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 adrenocorticotrophic 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 patients, especially 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 of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [see *Dosage and Administration* (2.1, 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 of 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 reduced metabolites.

Excretion

Only a small amount of the hydromorphone dose is excreted unchanged in the urine. Most of the dose is excreted as hydromorphone-3-glucuronide along with minor amounts of 6-hydroxy reduced 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_{0-8}) 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* (8.6)].

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_{0-8}) is increased by 2-fold in patients with moderate ($CL_{CR} = 40 - 80$ mL/min) renal impairment and increased by 4-fold in patients with 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). Start patients with renal impairment on