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

WARNING: RISK OF MEDICATION ERRORS, ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

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 addictions, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.2)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.3)**
- **Prolonged use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)**
- **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. Limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.5, 7).**

FRESENIUS KABI

451503c /Revised: November 2019

HYDROmorphone Hydrochloride
Injection
HYDROmorphone Hydrochloride
Injection [high potency formulation (HPF)]

Rx Only

RECENT MAJOR CHANGES

Warnings & Precautions (5.3)	11/2019

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 alternative 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 dosages 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, or at least 30 mg oral transdermal fentanyl per hour, or at least 30 mg of oral oxycodone per day, or 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 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, and misuse with opioids, even at recommended doses, reserve Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

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:
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 Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] and monitor 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)]. Monitor for respiratory depression, especially during initiation of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] or following a dose increase *[see Warnings and Precautions (5.3)]*.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.4)]*.

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 *[see Warnings and Precautions (5.5), Drug Interactions (7)]*.

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

1 INDICATIONS AND USAGE

Hydromorphone Hydrochloride Injection is indicated for the management of pain severe enough to require an opioid analgesic and for which alternate 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 30 mg oral transdermal fentanyl per hour, or at least 30 mg oral oxycodone per day, or at least 8 mg 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, and misuse with opioids, even at recommended doses *[see Warnings and Precautions (5.2)]*, reserve Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Always initiate dosing in opioid-naive patients using Hydromorphone Hydrochloride Injection. Never administer Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] to opioid-naive patients.
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.2)]*.
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) and adjust the dosage accordingly *[see Warnings and Precautions (5.3)]*.
- 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 in 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 of Hydromorphone Hydrochloride Injection is 1 mg to 2 mg every 2 to 3 hours as necessary. Depending on the clinical situation, the initial starting dose may be lowered in patients who are opioid naive *[see Warnings and Precautions (5.3)]*.

Intravenous Administration:
The initial starting dose is 0.2 to 1 mg every 2 to 3 hours. Intravenous administration should be slow, 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., 6 doses for every 4-hour dosing; 8 doses for every 3-hour dosing). Titrate the dose according to the patient's response.

Use Hydromorphone Hydrochloride Injection (HPF) ONLY for patients who require the higher concentration and lower total volume of Hydromorphone Hydrochloride Injection (HPF). Because of its high concentration, the delivery of precise doses of Hydromorphone Hydrochloride Injection (HPF) may be difficult if low doses of Hydromorphone are required. Therefore, use Hydromorphone Hydrochloride Injection (HPF) only if the amount of hydromorphone required can be delivered accurately with this formulation.

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
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 and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.2)]*. 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 unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

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 hypoxemia. 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)]*.

2.6 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 abruptly discontinue Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) in a physically-dependent patient *[see Warnings and Precautions (5.12), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Hydromorphone Hydrochloride Injection:
Each 1 mL 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 (5.3)]*.
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.10)]*
- Hypersensitivity to hydromorphone, hydromorphone salts, any other components of the product.

Hydromorphone Hydrochloride Injection [high potency formulation (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 more 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 mg 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 Addiction, 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) expose 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.

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 by drug abusers and people with addiction disorders and are subject to criminal diversion. 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 antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) 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 (HPF) [high potency formulation (HPF)], the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF), and adjust dosage accordingly.

To ensure safe and effective use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF), monitor patients for signs of sedation and respiratory depression, particularly when initiating therapy with Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF), and when Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) are given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.5)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.4 Neonatal Opioid Withdrawal Syndrome
Prolonged use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] 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 a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.5 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 or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). 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. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7) and Patient Counseling Information (17)]*.

5.6 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or 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 [high potency formulation (HPF)] contain hydromorphone, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

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)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.7 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.

5.8 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 pressure. Avoid the use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) in patients with circulatory shock.

5.9 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness
In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF).
Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) in patients with impaired consciousness or coma.

5.10 Risks of Use in Patients with Gastrointestinal Conditions
Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.
The hydromorphone in Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.11 Increased Risk of Seizures in Patients with Seizure Disorders
The hydromorphone in Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) therapy.

5.12 Withdrawal
Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)]. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms *[see Drug Interactions (7)]*.

When discontinuing Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)], in a physically-dependent patient, gradually taper the dosage *[see Dosage and Administration (2.6)]*. Do not abruptly discontinue Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) in these patients *[see Drug Abuse and Dependence (9.3)]*.

5.13 Risks When Driving and Operating Machinery
Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) and know how they will react to the medication *[see Patient Counseling Information (17)]*.

5.14 Sulfites
Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

5.15 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 the injection should be given very slowly. Rapid intravenous injection of opioid analgesics increases the possibility of side effects such as hypotension and respiratory depression *[see Dosage and Administration (2)]*.

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)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Interactions with Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.5)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.7)]*
- Severe Hypotension *[see Warnings and Precautions (5.8)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Withdrawal *[see Warnings and Precautions (5.12)]*

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 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 chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

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)	
Clinical Impact:	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.
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. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.3)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
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.
Examples:	phenelzine, 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

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.4)]*. There are no available data with Hydromorphone Hydrochloride Injection in pregnant women to inform a drug-associated risk for major birth defects and miscarriage.

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 *Data*]. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated 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 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics 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 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 (5.4)]*.

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 reported.

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 supraoccipital, checkerboard and split sternebrae, 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

Chronic use of opioids 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 (5.6)]*.

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)] contain hydromorphone hydrochloride, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.2)]*.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"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 of prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare providers. "Doctor shopping" (visiting several prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF), like other opioids, can be diverted for non-medical 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 re-evaluation 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 other central nervous system 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 chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation of a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a significant degree until after several days to weeks of continued opioid usage.

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 (HPF) is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, 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 Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] 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, 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)]*.

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 techniques.

The opioid antagonists, naloxone or nalmefene 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. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to hydromorphone overdose.

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.

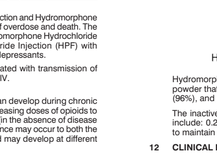
11 DESCRIPTION

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

Hydromorphone Hydrochloride Injection is available as a sterile, aqueous solution in single dose colorless vials for 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 4,5α-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, causing constipation. Other opioid-induced effects may include a reduction 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.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[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-Effect Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. 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 reduction 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 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$_\infty$) 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 tablet) are affected by renal impairment. Mean exposure to hydromorphone (C_{max} and AUC$_\infty$) is increased by 2-fold in patients with moderate (CLcr = 40 - 60 mL/min) renal impairment and increased by 4-fold in patients with severe (CLcr< 30 mL/min) renal impairment compared with normal subjects (CLcr> 80 mL/min). In addition, in patients with severe renal impairment, hydromorphone appeared to be more slowly eliminated with a longer terminal elimination half-life (40 hr) compared to patients with normal renal function (15 hr). Start patients with renal impairment on one-fourth to one-half the usual starting dose depending on the degree of impairment. Patients with renal impairment should be closely monitored during dose titration *[see Use in Specific Populations (8.7)]*.

Geriatric Population

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

Sex

Sex has little effect on the pharmacokinetics of hydromorphone. Females appear to have a higher C_{max} (25%) than males with comparable AUC0-24 values. The difference observed in C_{max} may not be clinically relevant.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

Hydromorphone was positive in the mouse lymphoma assay in the presence of metabolic activation, but was negative in the mouse lymphoma assay in the absence of metabolic activation. Hydromorphone produces neither was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames assay). Hydromorphone was not clastogenic in either the *in vitro* human lymphocyte chromosome aberration assay or the *in vivo* mouse micronucleus assay.

Impairment of Fertility

Reduced implantation sites and viable fetuses were noted at 2.1 times the human daily dose of 32 mg/day in a study in which female rats were treated with 7.5, 3.5, or 7 mg/kg/day hydromorphone hydrochloride (0.5, 1.1, or 2.1 times a human daily dose of 24 mg/day (HDD) based on body surface area) beginning 14 days prior to mating through Gestation Day 7 and male rats were treated with the same hydromorphone hydrochloride doses beginning 28 days prior to and throughout mating.

16 HOW SUPPLIED/STORAGE AND HANDLING

Hydromorphone Hydrochloride Injection

Hydromorphone Hydrochloride Injection is supplied in single dose colorless vials. Each mL of sterile, aqueous solution contains 1 mg, 2 mg, or 4 mg of hydromorphone hydrochloride with 0.2% sodium citrate and 0.2% citric acid solution. Hydromorphone Hydrochloride Injection is preservative free and is supplied as follows:

Product Code	Unit of Sale	Strength	Each
852101	NDC 63323-852-25 Unit of 25	1 mg per mL	NDC 63323-852-03 1 mL Single Dose Vial
853101	NDC 63323-853-25 Unit of 25	2 mg per mL	NDC 63323-853-03 1 mL Single Dose Vial
854101	NDC 63323-854-10 Unit of 25	4 mg per mL	NDC 63323-854-03 1 mL Single Dose Vial

Hydromorphone Hydrochloride Injection [high potency formulation (HPF)]

Hydromorphone Hydrochloride Injection (HPF) is supplied in single dose amber vials. Each single dose vial of sterile aqueous solution contains 10 mg of hydromorphone hydrochloride with 0.2% sodium citrate and 0.2% citric acid solution. Hydromorphone Hydrochloride Injection (HPF) is preservative free and is supplied as follows:

Product Code	Unit of Sale	Strength	Each
851101	NDC 63323-851-10 Unit of 10	10 mg per mL	NDC 63323-851-03 1 mL Single Dose Vial
851105	NDC 63323-851-15 Unit of 10	50 mg per 5 mL (10 mg per mL)	NDC 63323-851-07 5 mL Single Dose Vial
851150	NDC 63323-851-50 Individually Packaged	500 mg per 50 mL (10 mg per mL)	NDC 63323-851-50 50 mL Single Dose Vial

PROTECT FROM LIGHT.

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

Safety and Handling Instructions

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

17 PATIENT COUNSELING INFORMATION

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications, *[see Drug Interactions (7)]*.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6)]*.

Healthcare professionals can telephone Fresenius Kabi USA, LLC at 1-800-551-7176 for information or to report adverse events on this product.

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