HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HYDROMORPHONE HYDROCHLORIDE INJECTION and HYDROMORPHONE HYDROCHLORIDE injection (high potency formulation [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]) are for intravenous, intramuscular, or subcutaneous use.

Initial Dose: Intramuscular or Subcutaneous Use: The usual starting dose is 1 mg to 2 mg every 2 to 3 hours as necessary. (2.2)

Adrenal Insufficiency: The usual starting dose is 0.2 mg to 1 mg every 2 to 3 hours. The injection should be given slowly, over at least 2 to 3 minutes. (2.2)

Hydromorphone Hydrochloride Injection (high potency formulation [HPF]) is for opioid-tolerant patients only and should be used only if the amount of hydromorphone required can be delivered accurately with this formulation. (2.2)

Prolonged Use: 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 use of opioids 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. (3.3)

Concomitant Use: 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)

Boxed Warning

• Have not provided adequate analgesia, or are not expected to provide analgesia, to a patient (2.1)

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)

DOSAGE FORMS AND STRENGTHS

• Hydromorphone Hydrochloride Injection, 1 mg/mL, 2 mg/mL, or 4 mg/mL in single-dose vials and in Hydromorphone Hydrochloride Injection (high potency formulation [HPF]), 10 mg/mL in a 1 mL, 5 mL, and 50 mL single-dose amber vials. (3)

CONTRAINDICATIONS

• Significant respiratory depression, (4)

ADVERSE REACTIONS

• Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment, (4)

• Known or suspected gastrointestinal obstruction, including paralytic ileus, (4)

• Known hypersensitivity to hydromorphone, hydromorphone salts, sulfite-containing medications, or any other components of the product. (4)

• Hydromorphone Hydrochloride Injection (high potency formulation [HPF]): Patients who are not opioid tolerant. (4)

Warnings and Precautions

• Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease: Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) may precipitate respiratory arrest. (5.2)

• Neonatal Opioid Withdrawal Syndrome: Patients at or near term exposed to opioids from a high concentration, the delivery of precise doses of Hydromorphone Hydrochloride Injection (HPF) only if the amount of hydromorphone required can be delivered accurately with this formulation. (5.1)

• Discard any unused portion in an appropriate manner. (12.1)

• Patients with chronic pulmonary disease: Hydromorphone Hydrochloride Injection (HPF) may increase the frequency of seizures in patients with seizure disorder, (5.14)

• 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), (5.1)

• Carbon dioxide (CO2) retention from opioid-related adverse reactions. (5.14)

• Overestimating the Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) may increase the frequency of seizures in patients with seizure disorder, (5.14)

• Risks of Use in Patients with Increased Intracranial Pressure, Brain Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) in patients with impaired consciousness or coma. (5.9)

• Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) contain sodium metabisulfite. There is a risk of anaphylactic symptoms and life-threatening asthmaic episodes in susceptible people. (5.14)

ADVERSE REACTIONS

Most common adverse reactions are lightheadedness, dizziness, sedation, nausea, vomiting, sweating, flushing, dysphoria, euphoria, dry mouth, and diarrhea. (6.1)

To report Suspected Adverse Reactions, contact Fresenius Kabi USA, LLC at 1-800-651-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Serotonergic Drugs: Concomitant use may result in serotonin syndrome. (5.8)

Carbonic Anhydrase Inhibitors (MAOIs): Can potentiate the effects of Hydromorphone. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI. (5.8)

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) because they may reduce analgesic effect of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (HPF) or precipitate withdrawal symptoms. (5.8)

USE IN SPECIFIC POPULATIONS

• Pregnancy: May cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2018

5.7 Adrenal Insufficiency
5.9 Serotonin Syndrome
5.10 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness
5.11 Increased Risk of Seizures in Patients with Seizure Disorders
5.12 Withdrawal
5.13 Risks of Driving and Operating Machinery
5.14 Sulfites
5.15 Increased Risk of Hypotension and Respiratory Depression with Rapid Intraoperative Administration

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

9 DRUG ABUSE AND DEPENDENCE

8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
8.7 Renal Impairment

9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] is an opioid agonist indicated for use in opioid-tolerant patients who require profound sedation, respiratory depression, coma, and death [see Warnings and Precautions (5.5), Drug Interactions (7)].

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 to the minimum required.
• Follow patients for signs and symptoms of respiratory depression and sedation.

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses [see Warnings and Precautions (5.2), Drug Interactions (7)], reserve Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] for use in patients for whom alternative treatment options (e.g., non-narcotic 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
• NECTOSMART or equivalent treatment regimens

2 IMPORTANT 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 (5.4)].
• 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 (5.4)].
•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. 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 (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. In the clinical situation, the initial starting dose may be lowered in patients who are opioid naive.

Intravenous Administration:
The initial starting dose is 0.2 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 (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 previous opioid requirement when converting to 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.

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)].

2.5Titration and Maintenance of Therapy

Individually titrate Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection (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 experiences, as well as monitoring for the development of addiction, abuse, or misuse [see Warnings and Precautions (5.2), 5.4].

It 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.
HYDROMORPHONE HYDROCHLORIDE

Limitations of Use:
Hydromorphone Hydrochloride Injection is an opioid agonist indicated for intravenous, intramuscular, or subcutaneous use, CII [see Warnings and Precautions (5,1)]. Titrate the dose according to the patient's response. Hydromorphone Hydrochloride Injection (HPF) is contraindicated in patients who are not opioid tolerant (see Warnings and Precautions (5,1)).

5.3 Life-Threatening Respiratory Depression

Life-threatening respiratory depression may be 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)).

5.7 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with the use of opioids. Patients with adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, weight loss, hypotension, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing such as a ACTH stimulation test. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of cortisol. Weigh the patient and use a standard hCG or corticotropin (ACTH) injection 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 [high potency formulation (HPF)] may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose concomitant use of 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 for use in patients for whom alternative treatment options are inadequate. Observational studies have demonstrated that concomitant use of benzodiazepines and opioids increases the risk of drug-related mortality compared to opioid use alone. Benzodiazepines and other sedative-hypnotics, anxiolytics, and antidepressants are generally considered appropriate for use in patients that are opioid tolerant. Although severe hypotension may be more likely to occur in patients of advanced age and those with severe chronic respiratory disease, monitor patients closely for respiratory depression or hypotension.

5.5 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Because of the risks of addiction, abuse, and misuse with opioids, consider the need for risk evaluation and mitigation plans for patients receiving a long-term prescription for hydromorphone hydrochloride injection (HPF) (see boxed warning).

6. ADVERSE REACTIONS

There are no adequately controlled studies in ambulatory patients. There is increased risk in patients whose concomitant use of 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 for use in patients for whom alternative treatment options are inadequate. Observational studies have demonstrated that concomitant use of benzodiazepines and opioids increases the risk of drug-related mortality compared to opioid use alone. Benzodiazepines and other sedative-hypnotics, anxiolytics, and antidepressants are generally considered appropriate for use in patients that are opioid tolerant. Although severe hypotension may be more likely to occur in patients of advanced age and those with severe chronic respiratory disease, monitor patients closely for respiratory depression or hypotension.
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 CO2 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 CO2 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 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 of 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 Sulfoxide
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
Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent 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 rarely in patients treated with 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))

<table>
<thead>
<tr>
<th>Component</th>
<th>Clinical Impact</th>
<th>Intervention</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines and other Central Nervous System Depressants (CNS)</td>
<td>May reduce the analgesic effect of Hydromorphone Hydrochloride Injection and/or Hydromorphone Hydrochloride Injection (HPF) and/or precipitate withdrawal syndrome.</td>
<td>Avoid concomitant use.</td>
<td>Butorphanol, nalbuphine, pentazocine, buprenorphine</td>
</tr>
<tr>
<td>Serotonin Drugs</td>
<td>May reduce the analgesic effect of Hydromorphone Hydrochloride Injection and/or Hydromorphone Hydrochloride Injection (HPF) and/or precipitate withdrawal syndrome.</td>
<td>Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decreased dose of Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) and/or the muscle relaxant as necessary.</td>
<td>Morphine, fentanyl, tramadol, naltrexone, naltrexone enanthate</td>
</tr>
<tr>
<td>Monoamine Oxidase Inhibitors (MAOIs)</td>
<td>May reduce the analgesic effect of Hydromorphone Hydrochloride Injection and/or Hydromorphone Hydrochloride Injection (HPF) and/or precipitate withdrawal syndrome.</td>
<td>Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.</td>
<td>Metyrapone, tranylcypromine, isocarboxazid</td>
</tr>
</tbody>
</table>

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 (5.6)). 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 0.6 times the human daily dose of 24 mg/day (HDD), respectively. In published studies, neonatal side effects were noted following subsequent injection of hydromorphone to pregnant hamsters at doses 6.4 times the human daily dose (5.6) and at 6.4 times the human daily dose (5.6). Adverse effects were noted at 40 or 45 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 are taking, or plan to take serotonergic medications, syndrome and to seek medical attention right away if symptoms occur.

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

<table>
<thead>
<tr>
<th>Component</th>
<th>Clinical Impact</th>
<th>Intervention</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic Drugs</td>
<td>May reduce the analgesic effect of Hydromorphone Hydrochloride Injection and/or Hydromorphone Hydrochloride Injection (HPF) and/or precipitate withdrawal syndrome.</td>
<td>Monitor patients for signs of urinary retention and/or constipation, which may lead to paralytic ileus.</td>
<td>Butorphanol, nalbuphine, pentazocine, buprenorphine</td>
</tr>
</tbody>
</table>

Risks Specific to 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 (HPF) and other opioid analgesics, sedatives, tranquilizers, or other CNS depressants (see Warnings and Precautions (5.6)).

8.2 Nursing Mothers

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome (see Warnings and Precautions (5.6)). Hydromorphone Hydrochloride Injection and Hydromorphone Hydrochloride Injection (HPF) are used concomitantly with opioid drugs. Observe neonates for symptoms of neonatal opioid withdrawal syndrome and manage accordingly (see Warnings and Precautions (5.6)).

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 increase in the rate of uterine dilation, which proceeds to the fetal delivery. Monitor the mother and newborn for signs of respiratory depression and sedation.

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 1, 5, 10 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...
Less Frequently Observed Adverse Reactions

TABLE 1. Clinically Significant Drug Interactions with Hydromorphone

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines and other Central Nervous System Depressants (CNS)</td>
<td></td>
</tr>
</tbody>
</table>

The use of Hydromorphone Hydrochloride Injection or Hydromorphone Hydrochloride Injection [high potency formulation (HPF)] include respiratory depression and laryngospasm, dyspnea, oropharyngeal swelling. The inactive ingredients in Hydromorphone Hydrochloride Injection include lactic acid, sodium chloride, and polysorbate 80. [see Warnings and Precautions (5.4)].

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 a drug. Physical dependence 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 withdraw signs [see Use in Specific Populations (8.1)].
Cross Tech–83208–Proof 1

Table 1 includes clinically significant drug interactions with Serotonergic Drugs

<table>
<thead>
<tr>
<th>Symbol</th>
<th>If concomitant use is warranted, carefully observe the patient, apnea and, to a lesser degree, circulatory depression, respiratory</th>
</tr>
</thead>
</table>

Renal and urinary disorders:

- Hydromorphone Hydrochloride Injection [high potency formulation (HPF)]
- Examples: tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and Hydromorphone Hydrochloride Injection (HPF) are used to paralytic ileus.

The chemical name of Hydromorphone Hydrochloride is 4,5-epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride. The molecular weight is 321.80. Its molecular formula is C_{21}H_{24}NO_{3}HCl, and it has the following chemical structure:

\[
\text{H} \quad \text{N} \quad \text{CH}_3
\]

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 of 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 hydrocodone 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 receptor 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, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Hydromorphone produces peripheral vasoconstriction which may result in a decrease in blood pressure 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.

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 cause of opioid-induced 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 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 opioid analgesics. 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 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) 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 the 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), mean exposure to hydromorphone (C_{max} and AUC) is increased 4-fold in patients with moderate (Ccr = 40 - 60 mL/min) renal impairment and increased by 4-fold in patients with severe (Ccr < 30 mL/min) renal impairment compared with normal subjects (Ccr > 40 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 h) compared to patients with normal renal function (15 h). Start patients with renal impairment on one-fourth to one-half the usual starting dose depending on the degree of renal impairment. Patients with renal impairment should be closely monitored during dose titration [see Use in Specific Populations (8.7)].

Genetic 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 AUC-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 was not mutagenic in the in vitro bacterial reverse mutation assay (Ames assay). Hydromorphone was not clastogenic in either the in vitro human lymphocyte chromatin 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 orally with 1.7, 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 (NGD) 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.
Due to additive pharmacologic effect, the concomitant use of opioids with serotonergic drugs can increase the risk of hypotension, respiratory depression, and opioid toxicity (e.g., respiratory depression, coma) syndrome or opioid toxicity (e.g., respiratory depression, coma).

### 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:

<table>
<thead>
<tr>
<th>Product No.</th>
<th>NDC No.</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>851101</td>
<td>63323-851-10</td>
<td>10 mg per mL</td>
</tr>
<tr>
<td>851105</td>
<td>63323-851-15</td>
<td>50 mg per 5 mL (10 mg per mL)</td>
</tr>
<tr>
<td>851150</td>
<td>63323-851-50</td>
<td>500 mg per 50 mL (10 mg per mL)</td>
</tr>
</tbody>
</table>

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 1-800-951-7176 for information or to report adverse events on this product.