HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HYDROMORPHONE HYDROCHLORIDE TABLETS USP safely and effectively. See full prescribing information for HYDROMORPHONE HYDROCHLORIDE TABLETS USP.

HYDROMORPHONE HYDROCHLORIDE tablets USP, for oral use, CII
Initial U.S. Approval: January 1984

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

***See full prescribing information for complete boxed warning*.**

- **Hydromorphone hydrochloride tablets expose users to risks of addiction, 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)**
- **Accidental ingestion of hydromorphone hydrochloride tablets, especially by children, can result in a fatal overdose of hydromorphone. (5.3)**
- **Prolonged use of hydromorphone hydrochloride tablets 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)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	05/2017
Indications and Usage (1)	05/2017
Dosage and Administration (2)	05/2017
Contraindications (4)	05/2017
Warnings and Precautions (5)	05/2017

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

Hydromorphone hydrochloride tablets contain hydromorphone, an opioid agonist, and are indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

Limitations of Use (1)
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve hydromorphone hydrochloride tablets 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)
- Usual adult starting dose for hydromorphone hydrochloride tablets is 2 mg to 4 mg, orally, every 4 to 6 hours. (2.2)
- Hepatic Impairment: Initiate treatment with one-fourth to one-half the usual starting dose, depending on degree of hepatic impairment. (2.3)
- Renal Impairment: Initiate treatment with one-fourth to one-half the usual starting dose, depending on degree of renal impairment. (2.4)
- Do not stop hydromorphone hydrochloride tablets abruptly in a physically-dependent patient. (2.5)

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

- Hydromorphone hydrochloride tablets: 2 mg, 4 mg, 8 mg (3)

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

- Significant respiratory depression. (4)
- 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, or sulfite-containing medications. (4)

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

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.6)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.7)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of hydromorphone hydrochloride tablets in patients with circulatory shock. (5.8)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of hydromorphone hydrochloride tablets in patients with impaired consciousness or coma. (5.9)

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

Most common adverse reactions are lightheadedness, dizziness, sedation, nausea, vomiting, sweating, flushing, dysphoria, euphoria, dry mouth, and pruritus. (6)

To report Suspected Adverse Reactions, contact Mallinckrodt at 1-800-778-7898 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue hydromorphone hydrochloride tablets. If serotonin syndrome is suspected. (7)
- Monoamine Oxidase 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. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with hydromorphone hydrochloride tablets because they may reduce analgesic effect of hydromorphone hydrochloride tablets or precipitate withdrawal symptoms. (7)

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

- Pregnancy: May cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 07/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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FULL PRESCRIBING INFORMATION

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

Addiction, Abuse, and Misuse

Hydromorphone hydrochloride tablets expose 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 tablets, 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 tablets. Monitor for respiratory depression, especially during initiation of hydromorphone hydrochloride tablets or following a dose increase *[see Warnings and Precautions (5.3)]*.

Accidental Ingestion

Accidental ingestion of even one dose of hydromorphone hydrochloride tablets, especially by children, can result in a fatal overdose of hydromorphone *[see Warnings and Precautions (5.3)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of hydromorphone hydrochloride tablets 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 tablets 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 tablets are indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

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 tablets 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

- 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 to 72 hours of initiating therapy and following dosage increases with hydromorphone hydrochloride tablets and adjust the dosage accordingly *[see Warnings and Precautions (5.3)]*.

2.2 Initial Dosage

Initiating Treatment with Hydromorphone Hydrochloride Tablets
Initiate treatment with hydromorphone hydrochloride tablets in a dosing range of 2 mg to 4 mg, orally, every 4 to 6 hours.

Conversion from Other Opioids to Hydromorphone Hydrochloride Tablets
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 tablets. It is safer to underestimate a patient's 24-hour hydromorphone hydrochloride tablets dosage than to overestimate the 24-hour dosage and manage an adverse reaction due to overdose.

In general, it is safest to start hydromorphone hydrochloride tablets therapy by administering half of the usual starting dose every 4 to 6 hours for hydromorphone hydrochloride tablets. The dose of hydromorphone hydrochloride tablets can be gradually adjusted until adequate pain relief and acceptable side effects have been achieved *[see Dosage and Administration (2.4)]*.

Conversion from Hydromorphone Hydrochloride Tablets to Extended-Release Hydromorphone Hydrochloride
The relative bioavailability of hydromorphone hydrochloride tablets compared to extended-release hydromorphone hydrochloride is unknown, so conversion to extended-release tablets must be accompanied by close observation for signs of excessive sedation and respiratory depression.

2.3 Dosage Modifications in Patients with Hepatic Impairment

Initiate treatment with one-fourth to one-half the usual hydromorphone hydrochloride tablets starting dose depending on the degree of impairment *[see Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

2.4 Dosage Modifications in Patients with Renal Impairment

Initiate treatment with one-fourth to one-half the usual hydromorphone hydrochloride tablets starting dose depending on the degree of impairment *[see Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]*.

2.5 Titration and Maintenance of Therapy

Individually titrate hydromorphone hydrochloride tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving hydromorphone

hydrochloride tablets 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 tablets 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.

For chronic pain, doses should be administered around-the-clock. A supplemental dose of 5 to 15% of the total daily usage may be administered every two hours on an as-needed basis.

2.6 Discontinuation of Hydromorphone Hydrochloride Tablets

When a patient who has been taking hydromorphone hydrochloride tablets regularly and may be physically dependent no longer requires therapy with hydromorphone hydrochloride tablets, 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 and 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 tablets in a physically dependent patient *[see Warnings and Precautions (5.12), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

- 2 mg tablets (flat faced beveled edge white to off-white tablet with one side debossed “M”; other side debossed “2”)
- 4 mg tablets (flat faced beveled edge white to off-white tablet with one side debossed “M”; other side debossed “4”)
- 8 mg tablets (white to off-white arc triangle shaped tablet debossed with a bisected “M” on one side and a split “8” on the other side)

4 CONTRAINDICATIONS

Hydromorphone hydrochloride tablets are contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.6)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.6)]*
- 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, or sulfite-containing medications (e.g., anaphylaxis) *[see Warnings and Precautions (5.14), Adverse Reactions (6.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Accidental Overdose and Death due to Medication Errors

Dosing errors can result in accidental overdose and death. Ensure that the dose is communicated clearly and dispensed accurately.

5.2 Addiction, Abuse, and Misuse

Hydromorphone hydrochloride tablets contain hydromorphone, a Schedule II controlled substance. As an opioid, hydromorphone hydrochloride tablets 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 tablets. 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 tablets, and monitor all patients receiving hydromorphone hydrochloride tablets 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 tablets, but use in such patients necessitates intensive counseling about the risks and proper use of hydromorphone hydrochloride tablets 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 tablets. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. 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 tablets, 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 to 72 hours of initiating therapy with and following dosage increases of hydromorphone hydrochloride tablets.

To reduce the risk of respiratory depression, proper dosing and titration of hydromorphone hydrochloride tablets are essential *[see Dosage and Administration (2)]*.

Overestimating the hydromorphone hydrochloride tablets dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of hydromorphone hydrochloride tablets, especially by children, can result in respiratory depression and death due to an overdose of hydromorphone.

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of hydromorphone hydrochloride tablets 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 tablets 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 tablets are 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), Patient Counseling Information (17)]*.

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

The use of hydromorphone hydrochloride tablets 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 tablet-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of hydromorphone hydrochloride tablets *[see Warnings and Precautions (5.3)]*.

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

Monitor such patients closely, particularly when initiating and titrating hydromorphone hydrochloride tablets and when hydromorphone hydrochloride tablets 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 tablets 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 tablets. In patients with circulatory shock, hydromorphone hydrochloride tablets may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of hydromorphone hydrochloride tablets 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 tablets 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 tablets.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of hydromorphone hydrochloride tablets in patients with impaired consciousness or coma.

5.10 Risks of Use in Patients with Gastrointestinal Conditions

Hydromorphone hydrochloride tablets are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The hydromorphone in hydromorphone hydrochloride tablets 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 tablets 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 tablets 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 tablets. 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 tablets in a physically-dependent patient, gradually taper the dosage *[see Dosage and Administration (2.6)]*. Do not abruptly discontinue hydromorphone hydrochloride tablets in these patients *[see Drug Abuse and Dependence (9.3)]*.

5.13 Risks of Driving and Operating Machinery

Hydromorphone hydrochloride tablets 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 tablets and know how they will react to the medication.

5.14 Sulfites

Hydromorphone hydrochloride tablets 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. Use of hydromorphone hydrochloride tablets is contraindicated in patients with hypersensitivity to sulfite-containing medications.

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 or 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)]*

6.1 Clinical Trial Experience

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

Serious adverse reactions associated with hydromorphone hydrochloride tablets 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

Hepatobiliary disorders: biliary colic

Metabolism and nutrition disorders: decreased appetite

Musculoskeletal and connective tissue disorders: muscle rigidity

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

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

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

Respiratory, thoracic, and mediastinal disorders: bronchospasm, laryngospasm

Skin and subcutaneous tissue disorders: urticaria, rash, hyperhidrosis

Vascular disorders: flushing, hypotension, hypertension

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of hydromorphone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Confusional state, convulsions, drowsiness, dyskinesia, dyspnea, erectile dysfunction, fatigue, hepatic enzymes increased, hyperalgesia, hypersensitivity reaction, lethargy, myoclonus, oropharyngeal swelling, peripheral edema, and somnolence.

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 tablets.

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 tablets.

Table 1: Clinically Significant Drug Interactions with Hydromorphone Hydrochloride Tablets

Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or 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 tablets 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), 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 tablets 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 tablets and/or precipitate withdrawal symptoms.
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 tablets 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 tablets is 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 tablets 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 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 to 4% and 15 to 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 last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.4)]*.

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 tablets are 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 tablets, 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 tablets and any potential adverse effects on the breastfed infant from hydromorphone hydrochloride tablets or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to hydromorphone hydrochloride tablets 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 (6.2), Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of hydromorphone hydrochloride tablets in pediatric patients have 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 tablets 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 is affected by hepatic impairment. Due to increased exposure of hydromorphone, patients with 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 is affected by renal impairment. In addition, in patients with severe renal impairment, hydromorphone appeared to be more slowly eliminated with a longer terminal elimination half-life. 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 tablets contain hydromorphone, a Schedule II controlled substance.

9.2 Abuse

Hydromorphone hydrochloride tablets contain hydromorphone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, oxycodone, methadone, morphine, oxymorphone and tapentadol. Hydromorphone hydrochloride tablets 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 with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among 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 tablets, 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 Tablets
Hydromorphone hydrochloride tablets are for oral use only. Abuse of hydromorphone hydrochloride tablets poses a risk of overdose and death. The risk is increased with concurrent abuse of hydromorphone hydrochloride tablets 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 or 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 clinically significant degree until after several days to weeks of continued opioid usage.

Hydromorphone hydrochloride tablets should not be abruptly discontinued in a physically-dependent patient *[see Dosage and Administration (2.6)]*. If hydromorphone hydrochloride tablets are 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 tablets 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 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 action of hydromorphone in hydromorphone hydrochloride tablets, 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.

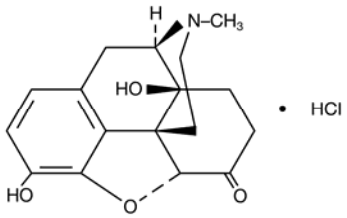
In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. 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 tablets, a hydrogenated ketone of morphine, is an opioid agonist.

Hydromorphone Hydrochloride Tablets USP are supplied in 2 mg, 4 mg, and 8 mg tablets for oral administration. The tablet strengths describe the amount of hydromorphone hydrochloride in each tablet.

The chemical name is 4,5α-epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride. It has the following chemical structure:



$C_{17}H_{19}NO_3 \cdot HCl$ MW = 321.80

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 2 mg, 4 mg, and 8 mg tablets contain the following inactive ingredients: lactose monohydrate, magnesium stearate, microcrystalline cellulose and stearic acid.

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 action 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 to 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 origins 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 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 (6.2)]*. 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 (6.2)]*.

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

Concentration-Efficacy Relationships
The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with 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, 2.5)]*.

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 (2.2, 2.3, 2.5)]*.

12.3 Pharmacokinetics

Absorption
The analgesic activity of hydromorphone hydrochloride tablets is due to the parent drug, hydromorphone. Hydromorphone is rapidly absorbed from the gastrointestinal tract after oral administration and undergoes extensive first-pass metabolism. Exposure of hydromorphone (C_{max} and AUC_{0-24}) is dose-proportional at a dose range of 2 and 8 mg. *In vivo* bioavailability following single-dose administration of the 8 mg tablet is approximately 24% (coefficient of variation 21%).

After oral administration of hydromorphone hydrochloride tablets, peak plasma hydromorphone concentrations are generally attained within ½ to 1 hour.

	Mean (%cv)			
Dosage Form	**C_{max} (ng)**	**T_{max} (hrs)**	**AUC (ng*hr/mL)**	**$T_{½}$ (hrs)**
8 mg Tablet	5.5 (33%)	0.74 (34%)	23.7 (28%)	2.6 (18%)

Food Effects
In a study conducted with a single 8 mg dose of hydromorphone (2 mg hydromorphone immediate-release tablets), food lowered C_{max} by 25%, prolonged T_{max} by 0.8 hour, and increased AUC by 35%. The effects may not be clinically relevant.

Distribution
At therapeutic plasma levels, hydromorphone is approximately 8 to 19% bound to plasma proteins. After an intravenous bolus dose, the steady state of volume 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.

Specific Populations

Hepatic Impairment
After oral administration of 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. Due to increased exposure of hydromorphone, patients with moderate hepatic impairment should be started at a lower dose and closely monitored during dose titration. Pharmacokinetics of hydromorphone in severe hepatic impairment patients has not been studied. Further increase in C_{max} and AUC of hydromorphone in this group is expected. As such, starting dose should be even more conservative *[see Use in Specific Populations (8.6)]*.

Renal Impairment
After oral administration of a single 4 mg dose (2 mg hydromorphone immediate-release tablets), exposure to hydromorphone (C_{max} and AUC_{0-48}) is increased in patients with impaired renal function by 2-fold in moderate (CLcr = 40 to 60 mL/min) and 3-fold in 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 longer terminal elimination half-life (40 hr) compared to patients with normal renal function (15 hr). Patients with moderate renal impairment should be started on a lower dose. Starting doses for patients with severe renal impairment should be even lower. Patients with renal impairment should be closely monitored during dose titration *[see Use in Specific Populations (8.7)]*.

Age: 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 higher C_{max} (25%) than males with comparable AUC_{0-24} 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 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 orally with 1.75, 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.

14 CLINICAL STUDIES

Analgesic effects of single doses of hydromorphone hydrochloride oral solution administered to patients with post-surgical pain have been studied in double-blind controlled trials. In one study, both 5 mg and 10 mg of hydromorphone hydrochloride oral solution provided significantly more analgesia than placebo. In another trial, 5 mg and 10 mg of hydromorphone hydrochloride oral solution were compared to 30 mg and 60 mg of morphine sulfate oral liquid. The pain relief provided by 5 mg and 10 mg hydromorphone hydrochloride oral solution was comparable to 30 mg and 60 mg oral morphine sulfate, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

Protect from light.

Hydromorphone Hydrochloride Tablets USP, 2 mg are available as a flat faced beveled edge white to off-white tablet with one side debossed “M”; other side debossed “2”.

Bottles of 100..... NDC 0406-3243-01

Hydromorphone Hydrochloride Tablets USP, 4 mg are available as a flat faced beveled edge white to off-white tablet with one side debossed “M”; other side debossed “4”.

Bottles of 100..... NDC 0406-3244-01

Hydromorphone Hydrochloride Tablets USP, 8 mg are available as a white to off-white arc triangle shaped tablet debossed with a bisected “M” on one side and a split “8” on the other side.

Bottles of 100..... NDC 0406-3249-01

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Addiction, Abuse, and Misuse
Inform patients that the use of hydromorphone hydrochloride tablets, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see*

Warnings and Precautions (5.2)]. Instruct patients not to share hydromorphone hydrochloride tablets with others and to take steps to protect hydromorphone hydrochloride tablets from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting hydromorphone hydrochloride tablets or when the dosage is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.3)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.3)]*. Instruct patients to take steps to store hydromorphone hydrochloride tablets securely and to dispose of unused hydromorphone hydrochloride tablets. When hydromorphone hydrochloride tablets are no longer needed, the unused medication should be destroyed by flushing it down the toilet.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if hydromorphone hydrochloride tablets are used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

Serotonin Syndrome

Inform patients that hydromorphone hydrochloride tablets 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)]*.

MAOI Interaction

Inform patients to avoid taking hydromorphone hydrochloride tablets while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking hydromorphone hydrochloride tablets *[see Drug Interactions (7)]*.

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.7)]*.

Important Administration Instructions

Instruct patients how to properly take hydromorphone hydrochloride tablets.

- Advise patients not to adjust the dose of hydromorphone hydrochloride tablets without consulting with a physician or other healthcare professional.
- If patients have been receiving treatment with hydromorphone hydrochloride tablets for more than a few weeks and cessation of therapy is indicated, counsel them on the importance of safely tapering the dose as abrupt discontinuation of the medication could precipitate withdrawal symptoms. Provide a dose schedule to accomplish a gradual discontinuation of the medication *[see Dosage and Administration (2.5, 2.6)]*.

Hypotension

Inform patients that hydromorphone hydrochloride tablets may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.8)]*.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in hydromorphone hydrochloride tablets. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of hydromorphone hydrochloride tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that hydromorphone hydrochloride tablets can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1), Warnings and Precautions (5.4)]*.

Lactation

Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs *[see Use in Specific Populations (8.2)]*.

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Population (8.3)]*.

Driving or Operating Heavy Machinery

Inform patients that hydromorphone hydrochloride tablets may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.13)]*.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6), Clinical Pharmacology (12.2)]*.

Disposal of Unused Hydromorphone Hydrochloride Tablets

Advise patients to flush unused hydromorphone hydrochloride tablets down the toilet.

Healthcare professionals can telephone Mallinckrodt Inc. at 1-800-778-7898 for information on this product.

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An electronic copy of this medication guide can be obtained from www.mallinckrodt.com/Medguide/MG20H29.pdf or by calling 1-800-778-7898 for alternate delivery options.

Medication Guide
Hydromorphone Hydrochloride (hy-dro-MOR-fone hy-dro-KLOR-īd) Tablets, CII

Hydromorphone hydrochloride tablets are:

- Strong prescription pain medicines that contains an opioid (narcotic) that is used to manage pain severe enough to require an opioid analgesic, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
- Opioid pain medicines that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about hydromorphone hydrochloride tablets:

- **Get emergency help right away if you take too many hydromorphone hydrochloride tablets (overdose).** When you first start taking hydromorphone hydrochloride tablets, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Taking hydromorphone hydrochloride tablets with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your hydromorphone hydrochloride tablets. They could die from taking them. Store hydromorphone hydrochloride tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away hydromorphone hydrochloride tablets is against the law.

Do not take hydromorphone hydrochloride tablets if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking hydromorphone hydrochloride tablets, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of hydromorphone hydrochloride tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Hydromorphone hydrochloride tablets pass into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking hydromorphone hydrochloride tablets with certain other medicines can cause serious side effects that could lead to death.

When taking hydromorphone hydrochloride tablets:

- Do not change your dose. Take hydromorphone hydrochloride tablets exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time.
- Call your healthcare provider if the dose you are taking does not control your pain.
- If you have been taking hydromorphone hydrochloride tablets regularly, do not stop taking hydromorphone hydrochloride tablets without talking to your healthcare provider.
- After you stop taking hydromorphone hydrochloride tablets flush any unused tablets down the toilet.

While taking hydromorphone hydrochloride tablets DO NOT:

- Drive or operate heavy machinery, until you know how hydromorphone hydrochloride tablets affect you. Hydromorphone hydrochloride tablets can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with hydromorphone hydrochloride tablets may cause you to overdose and die.

The possible side effects of hydromorphone hydrochloride tablets:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of hydromorphone hydrochloride tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

Manufactured by: SpecGx LLC, Webster Groves, MO 63119 USA, www.Mallinckrodt.com or call 1-800-778-7898

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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