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HYDROMORPHONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ®

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HYDROMORPHONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS safely and effectively. See full prescribing information for HYDROMORPHONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS.

HYDROMORPHONE HYDROCHLORIDE extended-release tablets, for oral use, CII

Initial U.S. Approval: 1984

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF HYDROMORPHONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS
See full prescribing information for complete boxed warning.

- **Hydromorphone hydrochloride extended-release tablets exposes 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. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow hydromorphone hydrochloride extended-release tablets whole to avoid exposure to a potentially fatal dose of hydromorphone. (5.2)**
- **Accidental ingestion of hydromorphone hydrochloride extended-release tablets, especially by children, can result in fatal overdose of hydromorphone. (5.2)**
- **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. (5.3, 7)**
- **Prolonged use of hydromorphone hydrochloride extended-release tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. 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. (5.4)**
- **To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.5)**

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

Dosage and Administration (2.2, 2.4)	10/2023
Warnings and Precautions (5.1, 5.2, 5.3, 5.6)	10/2023
Overdosage (10)	10/2023
Patient Counseling Information	10/2023

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

Hydromorphone hydrochloride extended-release tablets are an opioid agonist indicated for the management of severe and persistent pain that requires an extended treatment period with a daily opioid analgesic and for which alternative treatment options are inadequate.

Patients considered opioid tolerant are those who are taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or duration, and because of the greater risks of overdose and death with extended-release/long-acting opioid formulations, reserve hydromorphone hydrochloride extended-release tablets for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- Hydromorphone hydrochloride extended-release tablets are not indicated as an as-needed (prn) analgesic. (1)

----------DOSAGE AND ADMINISTRATION----------

- Hydromorphone hydrochloride extended-release tablets should be prescribed only by healthcare professionals who are knowledgeable about the use of extended-release/long-acting opioids and how to mitigate the associated risks. (2.1)
- For once daily administration IN OPIOID-TOLERANT PATIENTS. (2.1)
- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals. Reserve titration to higher doses of hydromorphone hydrochloride extended-release tablets for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks. (2.1, 5)
- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse (5.1)
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with hydromorphone hydrochloride extended-release tablets. Consider this risk when selecting an initial dose and when making dose adjustments (2.1, 5.2)
- Instruct patients to swallow hydromorphone hydrochloride extended-release tablets intact, and not to cut, break, chew, crush, or dissolve the tablets (risk of potentially fatal overdose). (2.1, 5.1)
- Discuss availability of naloxone with the patient and caregiver and assess each patient's need for access to naloxone, both when initiating and renewing treatment with hydromorphone hydrochloride extended-release tablets. Consider prescribing naloxone based on the patient's risk factors for overdose. [2.2, 5.1, 5.2, 5.3].
- Dose may be increased using increments of 4 to 8 mg every 3 to 4 days as needed to achieve adequate analgesia. (2.4)
- Do not abruptly discontinue hydromorphone hydrochloride extended-release tablets in a physically-dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.5, 5.13)
- Moderate Hepatic Impairment: Initiate treatment with 25% of the dose that would be prescribed for patients with normal hepatic function. Monitor closely for respiratory and central nervous system depression. (2.6)
- Moderate and Severe Renal Impairment: Initiate treatment in patients with moderate renal impairment with 50% and patients with severe renal impairment with 25% of the hydromorphone hydrochloride extended-release tablets dose that would be prescribed for patients with normal renal function. Monitor closely for respiratory and central nervous system depression. (2.7)

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

Extended-release tablets: 8 mg, 12 mg, 16 mg, 32 mg (3)

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

- Opioid non-tolerant patients (4)
- 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)
- Narrowed or obstructed gastrointestinal tract (4)
- Known hypersensitivity to any components including hydromorphone hydrochloride and sulfites (4, 5.14)

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

- Opioid-Induced Hyperalgesia and Allodynia: Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation. (5.6)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or Elderly Cachectic Debilitated Patients: Regularly evaluate closely, particularly during initiation and titration. (5.7)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.8)
- Severe Hypotension: Regularly evaluate during dose initiation and titration. Avoid use of hydromorphone hydrochloride extended-release tablets in patients with circulatory shock. (5.9)
- 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 extended-release tablets in patients with impaired consciousness or coma. (5.10)

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

Most common adverse reactions (incidence >10%) are: constipation, nausea, vomiting, somnolence, headache, and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Camber Pharmaceuticals Inc. at 1-866-495-8330 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 extended-release 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 extended-release tablets because they may reduce analgesic effect of hydromorphone hydrochloride extended-release tablets or precipitate withdrawal symptoms. (5.13, 7)

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

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not recommended. (8.2)
- Severe Hepatic Impairment: Use not recommended. (8.6)
- Severe Renal Impairment: Consider an alternate analgesic. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revision: 01/24

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF HYDROMORPHONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS

Addiction, Abuse, and Misuse

Because the use of hydromorphone hydrochloride extended-release tablets exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death, assess each patient's risk prior to prescribing and reassess all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of hydromorphone hydrochloride extended-release tablets, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of hydromorphone hydrochloride extended-release tablets are essential *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Accidental ingestion of even one dose of hydromorphone hydrochloride extended-release tablets, especially by children, can result in a fatal overdose of hydromorphone *[see Warnings and Precautions (5.2)]*.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of hydromorphone hydrochloride extended-release tablets and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

Neonatal Opioid Withdrawal Syndrome (NOWS)

If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of NOWS, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery *[see Warnings and Precautions (5.4)]*.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription *[see Warnings and Precautions (5.5)]*.

1 INDICATIONS AND USAGE

Hydromorphone hydrochloride extended-release tablets are indicated for the management of severe and persistent pain that requires an extended treatment period with a daily opioid analgesic and for which alternative treatment options are inadequate.

Patients considered opioid tolerant are those who are receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or duration, and because of the greater risks of overdose and death with extended-release/long-acting opioid formulations, *[see Warnings and Precautions (5.1)]*, reserve hydromorphone hydrochloride extended-release tablets for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- Hydromorphone hydrochloride extended-release tablets are not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

To avoid medication errors, prescribers and pharmacists must be aware that hydromorphone is available as both immediate-release 8 mg tablets and extended-release 8 mg tablets.

Hydromorphone hydrochloride extended-release tablets should be prescribed only by healthcare professionals who are knowledgeable about the use of extended-release/long-acting opioids and how to mitigate the associated risks.

Due to the risk of respiratory depression, hydromorphone hydrochloride extended-release tablets are only indicated for use in patients who are already opioid-tolerant. Discontinue or taper all other extended-release opioids when beginning hydromorphone hydrochloride extended-release tablets therapy. As hydromorphone hydrochloride extended-release tablets are only for use in opioid-tolerant patients, do not begin any patient on hydromorphone hydrochloride extended-release tablets as the first opioid.

Patients who are opioid-tolerant are those receiving, for one week or longer, at least 60 mg of oral morphine per day, at least 25 mcg transdermal fentanyl per hour, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day, at least 25 mg oral oxymorphone per day, at least 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*. Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of hydromorphone hydrochloride extended-release tablets for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.
- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with hydromorphone hydrochloride extended-release tablets. Consider this risk when selecting an initial dose and when making dose adjustments *[see Warnings and Precautions (5)]*.

Instruct patients to swallow hydromorphone hydrochloride extended-release tablets whole *[see Patient Counseling Information (17)]*. Crushing, chewing, or dissolving hydromorphone hydrochloride extended-release tablets will result in uncontrolled delivery of hydromorphone and can lead to overdose or death *[see Warnings and Precautions (5.1)]*.

2.2 Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with hydromorphone hydrochloride extended-release tablets *[see Warnings and Precautions (5.2), Patient Counseling Information (17)]*.

Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program).

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

Consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.

2.3 Initial Dosage

Conversion from Other Oral Hydromorphone Formulations to Hydromorphone Hydrochloride Extended-Release Tablets

Patients receiving oral immediate-release hydromorphone may be converted to hydromorphone hydrochloride extended-release tablets by administering a starting dose equivalent to the patient's total daily oral hydromorphone dose, taken once daily.

Conversion from other oral opioids to Hydromorphone Hydrochloride Extended-Release Tablets

When hydromorphone hydrochloride extended-release tablets therapy is initiated, discontinue all other opioid analgesics other than those used on an as needed basis for breakthrough pain when appropriate.

There is substantial inter-patient variability in the relative potency of different opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of hydromorphone hydrochloride extended-release tablets. It is safer to underestimate a patient's 24-hour oral hydromorphone dosage and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral hydromorphone dosage and manage an adverse reaction due to overdose.

In an hydromorphone hydrochloride extended-release tablets clinical trial with an open-label titration period, patients were converted from their prior opioid to hydromorphone hydrochloride extended-release tablets using the **Table 1** as a guide for the initial hydromorphone hydrochloride extended-release tablets dose. The recommended starting dose of hydromorphone hydrochloride extended-release tablets are 50% of the calculated estimate of daily hydromorphone requirement. Calculate the estimated daily hydromorphone requirement using **Table 1**.

Consider the following when using the information in **Table 1**:

- This is **not** a table of equianalgesic doses.
- The conversion factors in this table are only for the conversion **from** one of the listed oral opioid analgesics **to** hydromorphone hydrochloride extended-release tablets.
- The table **cannot** be used to convert **from** hydromorphone hydrochloride extended-release tablets to another opioid. Doing so will result in an overestimation of the dose of the new opioid and may result in fatal overdose.

Table 1.
Conversion Factors to Hydromorphone Hydrochloride Extended-Release Tablets

Prior Oral Opioid	Approximate Oral Conversion Factor
Hydromorphone	1
Codeine	0.06
Hydrocodone	0.4
Methadone	0.6
Morphine	0.2
Oxycodone	0.4
Oxymorphone	0.6

To calculate the estimated hydromorphone hydrochloride extended-release tablets dose using **Table 1**:

- For patients on a single opioid, sum the current total daily dose of the opioid and then multiply the total daily dose by the conversion factor to calculate the approximate oral hydromorphone daily dose.
- For patients on a regimen of more than one opioid, calculate the approximate oral hydromorphone dose for each opioid and sum the totals to obtain the approximate total hydromorphone daily dose.
- For patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products in the conversion.

Always round the dose down, if necessary, to the appropriate hydromorphone hydrochloride extended-release tablets strength(s) available.

Example conversion from a single opioid to hydromorphone hydrochloride extended-release tablets:

Step 1: Sum the total daily dose of the opioid
- 30 mg of oxycodone 2 times daily = 60 mg total daily dose of oxycodone

Step 2: Calculate the approximate equivalent dose of oral hydromorphone based on the total daily dose of the current opioid using **Table 1**
- 60 mg total daily dose of oxycodone x Conversion Factor of 0.4 = 24 mg of oral hydromorphone daily

Step 3: Calculate the approximate starting dose of hydromorphone hydrochloride extended-release tablets to be given every 24 hours, which is 50% of the calculated oral hydromorphone dose. Round down, if necessary, to the appropriate hydromorphone hydrochloride extended-release tablet strengths available.
- 50% of 24 mg results in an initial dose of 12 mg of hydromorphone hydrochloride extended-release tablets once daily
- Adjust individually for each patient

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal or for signs of over-sedation/toxicity after converting patients to hydromorphone hydrochloride extended-release tablets.

Conversion from Transdermal Fentanyl to hydromorphone hydrochloride extended-release tablets

Eighteen hours following the removal of the transdermal fentanyl patch, hydromorphone hydrochloride extended-release tablets treatment can be initiated. To calculate the 24-hour hydromorphone hydrochloride extended-release tablets dose, use a conversion factor of 25 mcg/hr fentanyl transdermal patch to 12 mg of hydromorphone hydrochloride extended-release tablets. Then reduce the hydromorphone hydrochloride extended-release tablets dose by 50%.

For example:

Step 1: Identify the dose of transdermal fentanyl.
- 75 mg of transdermal fentanyl

Step 2: Use the conversion factor of 25 mcg/hr fentanyl transdermal patch to 12 mg of hydromorphone hydrochloride extended-release tablets.
- 75 mg of transdermal fentanyl: 36 mg total daily dose of hydromorphone hydrochloride extended-release tablets

Step 3: Calculate the approximate starting dose of hydromorphone hydrochloride extended-release tablets to be given every 24 hours, which is 50% of the converted dose. Round down, if necessary, to the appropriate hydromorphone hydrochloride extended-release tablet strengths available.
- 50% of 36 mg results in an initial dose of 18 mg, which would be rounded down to 16 mg of hydromorphone hydrochloride extended-release tablets once daily
- Adjust individually for each patient

Conversion from Methadone to Hydromorphone Hydrochloride Extended-Release Tablets

Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

2.4 Titration and Maintenance of Therapy

Individually titrate hydromorphone hydrochloride extended-release tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving hydromorphone hydrochloride extended-release tablets to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and other adverse reactions, as well as to reassess for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1, 5.13)]*. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During use of opioid therapy for an extended period of time, periodically reassess the continued need for use of opioid analgesics.

Plasma levels of hydromorphone hydrochloride extended-release tablets are sustained for 18 to 24 hours. Dosage adjustments of hydromorphone hydrochloride extended-release tablets may be made in increments of 4 to 8 mg every 3 to 4 days as needed to achieve adequate analgesia.

Patients who experience breakthrough pain may require a dose increase of hydromorphone hydrochloride extended-release tablets, or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the hydromorphone hydrochloride extended-release tablets dose.

If after increasing the dosage, unacceptable opioid-related adverse reactions are observed (including an increase in pain after dosage increase), consider reducing the dosage *[see Warnings and Precautions (5)]*. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.5 Safe Reduction or Discontinuation of Hydromorphone Hydrochloride Extended-Release Tablets

Do not abruptly discontinue hydromorphone hydrochloride extended-release tablets in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking hydromorphone hydrochloride extended-release tablets, there are a variety of factors that should be considered, including the total daily dose of opioid (including hydromorphone hydrochloride extended-release tablets) the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow-up plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with comorbid pain and substance use disorders may benefit from referral to a specialist.

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on hydromorphone hydrochloride extended-release tablets who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include 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. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, evaluate patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for an extended period of time, and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic *[see Warnings and Precautions (5.13), Drug Abuse and Dependence (9.3)]*.

2.6 Dosage Modifications in Patients with Moderate Hepatic Impairment

Start patients with moderate hepatic impairment on 25% of the hydromorphone hydrochloride extended-release tablets dose that would be prescribed for patients with normal hepatic function. Closely monitor patients with moderate hepatic impairment for respiratory and central nervous system depression during initiation of therapy with hydromorphone hydrochloride extended-release tablets and during dose titration. Use of alternate analgesics is recommended for patients with severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

2.7 Dosage Modifications in Patients with Renal Impairment

Start patients with moderate renal impairment on 50% of the hydromorphone hydrochloride extended-release tablets dose that would be prescribed for patients with normal renal function. Closely monitor patients with renal impairment for respiratory and central nervous system depression during initiation of therapy with hydromorphone hydrochloride extended-release tablets and during dose titration. As hydromorphone hydrochloride extended-release tablets are only intended for once daily administration, consider use of an alternate analgesic that may permit more flexibility with the dosing interval in patients with severe renal impairment *[see Use in Specific Populations (8.7)]*.

3 DOSAGE FORMS AND STRENGTHS

Extended-release tablets: available in 8 mg, 12 mg, 16 mg or 32 mg dosage strengths.

8 mg tablets: Light pink to pink film coated round, biconvex tablets printed with "266" in black ink on one side of the tablet.

12 mg tablets: Light yellow to yellow film coated, round, biconvex tablets printed with "267" in black ink on one side of the tablet.

16 mg tablets: Light beige to beige film coated, round, biconvex tablets printed with "268" in black ink on one side of the tablet.

32 mg tablets: White to off white film coated, round, biconvex tablets printed with "269" with black ink on one side of the tablet.

4 CONTRAINDICATIONS

Hydromorphone hydrochloride extended-release tablets are contraindicated in:

- Opioid non-tolerant patients. Fatal respiratory depression could occur in patients who are not opioid tolerant.
- Patients with significant respiratory depression *[see Warnings and Precautions (5.2)]*.
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.7)]*.
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.11)]*.
- Patients who have had surgical procedures and/or underlying disease resulting in narrowing of the gastrointestinal tract, or have "blind loops" of the gastrointestinal tract or gastrointestinal obstruction *[see Warnings and Precautions (5.11)]*.
- Patients with hypersensitivity (e.g., anaphylaxis) to hydromorphone *[see Warnings and Precautions (5.14)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

Hydromorphone hydrochloride extended-release tablets contains hydromorphone, a Schedule II controlled substance. As an opioid, hydromorphone hydrochloride extended-release tablets exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*. As modified-release products such as hydromorphone hydrochloride extended-release tablets deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of hydromorphone present.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed hydromorphone hydrochloride extended-release tablets and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing hydromorphone hydrochloride extended-release tablets, and reassess all patients receiving hydromorphone hydrochloride extended-release 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 addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of hydromorphone hydrochloride extended-release tablets for the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as hydromorphone hydrochloride extended-release tablets, but use in such patients necessitates intensive counseling about the risks and proper use of hydromorphone hydrochloride extended-release tablets along with frequent reevaluation for signs of addiction, abuse, and misuse. Consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

Abuse or misuse of hydromorphone hydrochloride extended-release tablets by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of hydromorphone and can result in overdose and death *[see Overdosage (10)]*.

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing hydromorphone hydrochloride extended-release tablets. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on careful storage of the drug during the course of treatment and proper disposal of unused drug. 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.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression from opioid use, 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 extended-release tablets, the risk is greatest during the initiation of therapy or following a dosage increase.

To reduce the risk of respiratory depression, proper dosing and titration of hydromorphone hydrochloride extended-release tablets are essential *[see Dosage and Administration (2)]*. Overestimating the hydromorphone hydrochloride extended-release tablets dose when converting patients from another opioid product can result in fatal overdose with the first dose.

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

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose *[see Patient Counseling Information (17)]*.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration (2.5)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with hydromorphone hydrochloride extended-release tablets.

Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (e.g., by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered *[see Patient Counseling Information (17)]*.

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone. *[see Warnings and Precautions (5.1, 5.3, Patient Counseling Information (17); Overdosage (10)]*.

5.3 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 extended-release tablets with benzodiazepines and/or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

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

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

If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose *[see

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HYDROMORPHONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS Ⓒ

Intervention:	The use of hydromorphone hydrochloride extended-release tablets are 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 extended-release tablets and/or precipitate withdrawal symptoms *[see Warnings and Precautions (5.13)]*.
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 *[see Warnings and Precautions (5.3)]*.
Intervention:	Because respiratory depression may be greater than otherwise expected, decrease the dosage of hydromorphone hydrochloride extended-release tablets and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Evaluate patients for signs for 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:	Evaluate patients for signs of urinary retention or reduced gastric motility when hydromorphone hydrochloride extended-release tablets are used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of opioid analgesics for an extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.4)]*. There are no adequate and well-controlled studies in pregnant women. Based on animal data, advise pregnant women of the potential risk to a fetus.

In animal reproduction studies, reduced postnatal survival of pups, developmental delays, and altered behavioral responses were noted following oral treatment of pregnant rats with hydromorphone during gestation and through lactation at doses 2.1 times the human daily dose of 32 mg/day (HDD), respectively. In published studies, neural tube defects were noted following subcutaneous injection of hydromorphone to pregnant hamsters at doses 4.8 times the HDD and soft tissue and skeletal abnormalities were noted following subcutaneous continuous infusion of 2.3 times the HDD to pregnant mice. No malformations were noted at 2.1 or 17 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

Use of opioid analgesics for an extended period of time during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, and manage accordingly *[see Warnings and Precautions (5.4)]*.

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 extended-release tablets are not recommended for use in pregnant women during or immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including hydromorphone hydrochloride extended-release 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 1.75, 3.5, or 7 mg/kg/day (0.5, 1.1, or 2.1 times the HDD of 32 mg/day 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 6 to 20 via oral gavage doses of 10, 25, or 50 mg/kg/day (4.3, 8.5, or 17 times the HDD of 32 mg/day based on body surface area, respectively). Maternal toxicity was noted in the highest dose group (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 (4.8 to 65.4 times the HDD of 32 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 (3.5 times the human daily dose of 32 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 (1.1, 2.3, or 4.6 times the human daily dose of 32 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 2.3 times the human dose of 32 mg/day based on body surface area. The findings cannot be clearly attributed to maternal toxicity.

Pregnant rats were treated with hydromorphone hydrochloride from Gestation Day 6 to Lactation Day 21 via oral gavage doses of 1.75, 3.5, or 7 mg/kg/day (0.5, 1.1, or 2.1 times the HDD of 32 mg/day based on body surface area, respectively). Reduced pup weights were noted at 1.1 and 2.1 times the human daily dose of 32 mg/day and increased pup deaths, delayed ear opening, reduced auditory startle reflex, and reduced open-field activity were also noted at 2.1 times the HDD. Maternal toxicity was noted in all treatment groups (reduced food consumption and body weights in all groups) and decreased maternal care in the high dose group.

8.2 Lactation

Risk Summary

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with hydromorphone hydrochloride extended-release tablets. Low concentrations of hydromorphone have been detected in human milk in clinical trials. Withdrawal symptoms can occur in breastfeeding infants when maternal administration of an opioid analgesic is stopped. Nursing should not be undertaken while a patient is receiving hydromorphone hydrochloride extended-release tablets since hydromorphone is excreted in the milk.

Clinical Considerations

Monitor infants exposed to hydromorphone hydrochloride extended-release tablets through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Use of opioids for an extended period of time may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of hydromorphone hydrochloride extended-release tablets in patients 17 years of age and younger 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 extended-release tablets slowly in geriatric patients and frequently reevaluate the patient for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.2)]*.

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 regularly evaluate renal function.

8.6 Hepatic Impairment

In a study that used a single 4 mg oral dose of immediate-release hydromorphone tablets, four-fold increases in plasma levels of hydromorphone (C_{max} and $AUC_{0-\infty}$) were observed in patients with moderate hepatic impairment (Child-Pugh Group B). Start patients with moderate hepatic impairment on 25% of the hydromorphone hydrochloride extended-release tablets dose that would be used in patients with normal hepatic function. Closely monitor patients with moderate hepatic impairment for respiratory and central nervous system depression during initiation of therapy with hydromorphone hydrochloride extended-release tablets and during dose titration. The pharmacokinetics of hydromorphone in severe hepatic impairment patients have not been studied. As further increases in C_{max} and $AUC_{0-\infty}$ of hydromorphone in this group are expected, use of alternate analgesics is recommended *[see Dosage and Administration (2.6)]*.

8.7 Renal Impairment

Administration of a single 4 mg dose of immediate-release hydromorphone tablets resulted in two-fold and four-fold increases in plasma levels of hydromorphone (C_{max} and AUC_{0-48h}) in moderate (CLcr = 40 to 60 mL/min) and severe (CLcr < 30 mL/min) impairment, respectively. In addition, in patients with severe renal impairment hydromorphone appeared to be more slowly eliminated with longer terminal elimination half-life. Start patients with moderate renal impairment on 50% and patients with severe renal impairment on 25% of the hydromorphone hydrochloride extended-release tablets dose that would be prescribed for patients with normal renal function. Closely monitor patients with renal impairment for respiratory and central nervous system depression during initiation of therapy with hydromorphone hydrochloride extended-release tablets and during dose titration. As hydromorphone hydrochloride extended-release tablets are only intended for once daily administration, consider use of an alternate analgesic that may permit more flexibility with the dosing interval in patients with severe renal impairment *[see Dosage and Administration (2.7)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Hydromorphone hydrochloride extended-release tablets contains hydromorphone, a Schedule II controlled substance.

9.2 Abuse

Hydromorphone hydrochloride extended-release tablets contains hydromorphone, a substance with high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction *[see Warnings and Precautions (5.1)]*.

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

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

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

Misuse and abuse of hydromorphone hydrochloride extended-release tablets increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of hydromorphone hydrochloride extended-release tablets with alcohol and other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of hydromorphone hydrochloride extended-release tablets abuse include those with a history of prolonged use of any opioid, including products containing hydromorphone, those with a history of drug or alcohol abuse, or those who use hydromorphone hydrochloride extended-release tablets in combination with other abused drugs.

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

Hydromorphone hydrochloride extended-release tablets, like other opioids, can be diverted for nonmedical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

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

Risks Specific to Abuse of Hydromorphone Hydrochloride Extended-Release Tablets

Abuse of hydromorphone hydrochloride extended-release tablets poses a risk of overdose and death. The risk is increased with concurrent use of hydromorphone hydrochloride extended-release tablets with alcohol and/or other CNS depressants.

Hydromorphone hydrochloride extended-release tablets is approved for oral use only. Inappropriate intravenous, intramuscular, or subcutaneous use of hydromorphone hydrochloride extended-release tablets can result in death, local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, and valvular heart injury, and embolism.

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

9.3 Dependence

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

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

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

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

Do not abruptly discontinue hydromorphone hydrochloride extended-release tablets in a patient physically dependent on opioids. Rapid tapering of hydromorphone hydrochloride extended-release tablets in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing hydromorphone hydrochloride extended-release tablets, gradually taper the dosage using a patient-specific plan that considers the following: the dose of hydromorphone hydrochloride extended-release tablets the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for an extended period of time at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper *[see Dosage and Administration (2.5), and Warnings and Precautions (5.13)]*.

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 extended-release 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, hypoglycemia, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

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 measures.

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

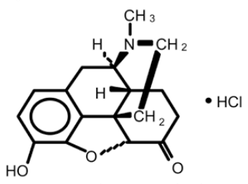
Because the duration of reversal is expected to be less than the duration of action of hydromorphone in hydromorphone hydrochloride extended-release tablets, carefully monitor the patient until spontaneous respiration is reliably reestablished. Hydromorphone hydrochloride extended-release tablets will continue to release hydromorphone and add to the hydromorphone load for up to 24 to 48 hours or longer following ingestion, necessitating prolonged monitoring. If the response to 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 extended-release tablets are for oral use and contain hydromorphone hydrochloride, an opioid agonist.

Hydromorphone hydrochloride USP is 4,5α-epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride. 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. Its empirical formula is $C_{17}H_{19}NO_3$•HCl. The compound has the following structural formula:



Hydromorphone hydrochloride extended-release tablets also contains the following inactive ingredients: Polyethylene Oxide, Povidone, butylated hydroxytoluene, Isopropyl Alcohol, Magnesium Stearate, Sodium Chloride, Hydroxypropyl Methyl Cellulose, Ferric Oxide Yellow, Acetone, Cellulose acetate, Polyethylene glycol, hypromellose and titanium dioxide

The 8 mg, 12 mg and 16 mg also contains iron oxide yellow and polysorbate. The 32 mg also contains talc, black iron oxide and propylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hydromorphone, a semi-synthetic morphine derivative, is a hydrogenated ketone of morphine.

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

CNS Depressant/Alcohol Interaction

Additive pharmacodynamic effects may be expected when hydromorphone hydrochloride extended-release tablets are used in conjunction with alcohol, other opioids, legal or illicit drugs that cause central nervous system depression.

Effects on the Central Nervous System

Hydromorphone produces dose-related 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 pathognomic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis, rather than miosis, may be seen due to severe hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Hydromorphone causes a reduction in motility associated with an increase in 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 is 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. Release of histamine may be induced by hydromorphone and can contribute to opioid-induced hypotension. Manifestations of histamine release or peripheral vasodilation may include pruritus, flushing, red eyes, sweating and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Use of opioids for an extended period of time may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

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 opioid agonists. The minimum effective analgesic concentration of hydromorphone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance *[see Dosage and Administration (2.1), (2.4)]*.

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), (2.3), (2.4)]*.

12.3 Pharmacokinetics

Absorption

Hydromorphone hydrochloride extended-release tablets are an extended-release formulation of hydromorphone that produces a gradual increase in hydromorphone concentrations. Following a single-dose administration of hydromorphone hydrochloride extended-release tablets, plasma concentrations gradually increase over 6 to 8 hours, and thereafter concentrations are sustained for approximately 18 to 24 hours post-dose. The median T_{max} values ranged from 12 to 16 hours. The mean half-life was approximately 11 hours, ranging from 8 to 15 hours in most individual subjects. Linear pharmacokinetics has been demonstrated for hydromorphone hydrochloride extended-release tablets over the dose range 8 to 64 mg, with a dose-proportional increase in C_{max} and overall exposure ($AUC_{0-\infty}$) (*see* **Table 5**). Steady-state plasma concentrations are approximately twice those observed following the first dose, and steady state is reached after 3 to 4 days of once-daily dosing of hydromorphone hydrochloride extended-release tablets. At steady state, hydromorphone hydrochloride extended-release tablets given once daily maintained hydromorphone plasma concentrations within the same concentration range as the immediate-release tablet given 4 times daily at the same total daily dose and diminished the fluctuations between peak and trough concentrations seen with the immediate-release tablet (*see* **Figure 1**). The bioavailability of hydromorphone hydrochloride extended-release tablets once daily and immediate-release hydromorphone four times daily in adults is comparable, as presented in **Table 5**.

Figure 1.
Mean Steady-State Plasma Concentration Profile

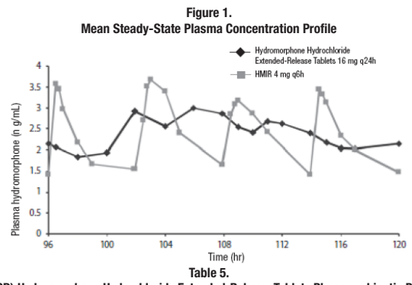


Table 5.
Mean (±SD) Hydromorphone Hydrochloride Extended-Release Tablets Pharmacokinetic Parameters

Regimen	Dosage	T_{max}* (hrs)	C_{max} (ng/mL)	AUC (ng·hr/mL)	$T_{½}$ (hr)
Single Dose (N = 31)	8 mg	12 (4-30)	0.93 (1.01)	18.1 (5.8)	10.6 (4.3)
	16 mg	16 (6-30)	1.69 (0.78)	36.5 (11.3)	10.3 (2.4)
	32 mg	16 (4-24)	3.25 (1.37)	72.2 (24.3)	11.0 (3.2)
	64 mg	16 (6-30)	6.61 (1.75)	156.0 (30.6)	10.9 (3.8)
Multiple Dose† (N = 29)	16 mg q24h	12 (6-24)	3.54 (0.96)‡	57.6 (16.3)	NA
	IR 4 mg q6h	0.75 (0.5-2)	5.28 (1.37)§	54.8 (14.8)	NA

NA = not applicable
* Median (range) reported for T_{max}
† Steady-state results on Day 5 (0-24 hours)
‡ C_{min} 2.15 (0.87) ng/mL
§ C_{min} 1.47 (0.42) ng/ML

Food Effect

The pharmacokinetics of hydromorphone hydrochloride extended-release tablets are not affected by food as indicated by bioequivalence when administered under fed and fasting conditions. Therefore, hydromorphone hydrochloride extended-release tablets may be administered without regard to meals. When a 16 mg dose of hydromorphone hydrochloride extended-release tablets was administered to healthy volunteers immediately following a high-fat meal, the median time to C_{max} (T_{max}) was minimally affected by the high-fat meal occurring at 16 hours compared to 18 hours while fasting.

Distribution

Following intravenous administration of hydromorphone to healthy volunteers, the mean volume of distribution was 2.9 (±1.3) L/kg, suggesting extensive tissue distribution. The mean extent of binding of hydromorphone to human plasma proteins was determined to be 27% in an *in vitro* study.

Elimination

Metabolism

After oral administration of an immediate-release formulation, hydromorphone undergoes extensive first-pass metabolism and is metabolized primarily in the liver by glucuronidation to hydromorphone-3-glucuronide, which follows a similar time course to hydromorphone in plasma. Exposure to the glucuronide metabolite is 35 to 40 times higher than exposure to the parent drug. *In vitro* data suggest that hydromorphone in clinically relevant concentrations has minimal potential to inhibit the activity of human hepatic CYP450 enzymes including CYP1A2, 2C9, 2C19, 2D6, 3A4, and 4A11.

Excretion

Approximately 75% of the administered dose is excreted in urine. Most of the administered hydromorphone dose is excreted as metabolites. Approximately 7% and 1% of the dose are excreted as unchanged hydromorphone in urine and feces, respectively.

Specific Populations

Age: Geriatric Patients

Population PK analysis performed on plasma concentration data from 407 osteoarthritis (OA) patients using hydromorphone hydrochloride extended-release tablets showed an average 11% increase in hydromorphone AUC in the elderly group (65 to 75 years of age) when compared to the younger age group (less than or equal to 65 years of age).

Sex

Females appeared to have approximately 10% higher mean systemic exposure in terms of C_{max} and AUC values.

Hepatic Impairment

In a study that used a single 4 mg oral dose of immediate-release hydromorphone tablets, four-fold increases in plasma levels of hydromorphone (C_{max} and $AUC_{0-\infty}$) were observed in patients with moderate hepatic impairment (Child-Pugh Group B). Pharmacokinetics of hydromorphone in severe hepatic impairment patients has not been studied. Further increase in C_{max} and $AUC_{0-\infty}$ of hydromorphone in this group is expected. Start patients with moderate hepatic impairment on 25% of the usual dose of hydromorphone hydrochloride extended-release tablets and closely monitor for respiratory and central nervous system depression during dose titration. Consider alternate analgesic therapy for patients with severe hepatic impairment *[see Dosage and Administration (2.6) and Specific Populations (8.6)]*.

Renal Impairment

Renal impairment affected the pharmacokinetics of hydromorphone and its metabolites following administration of a single 4 mg dose of immediate-release tablets. The effects of renal impairment on hydromorphone pharmacokinetics were two-fold and four-fold increases in plasma levels of hydromorphone (C_{max} and AUC_{0-48h}) in moderate (CLcr = 40 to 60 mL/min) and severe (CLcr < 30 mL/min) impairment, respectively. 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 subjects with normal renal function (15 hr). Start patients with moderate renal impairment on 50% of the usual hydromorphone hydrochloride extended-release tablets dose for patients with normal renal function and closely monitor for respiratory and central nervous system depression during dose titration. As hydromorphone hydrochloride extended-release tablets are only intended for once-daily administration, consider use of an alternate analgesic that may permit more flexibility with the dosing interval in patients with severe renal impairment *[see Dosage and Administration (2.7) and Use in Specific Populations (8.7)]*.

Drug Interaction Studies

Alcohol Interaction

An *in vivo* study examined the effect of alcohol (40%, 20%, 4% and 0%) on the bioavailability of a single dose of 16 mg of hydromorphone hydrochloride extended-release tablets in healthy, fasted or fed volunteers. The results showed that the hydromorphone mean $AUC_{0-\infty}$ was 5% higher and 4% lower (not statistically significant) in the fasted and fed groups respectively after co-administration of 240 mL of 40% alcohol. The $AUC_{0-\infty}$ was similarly unaffected in subjects following the co-administration of hydromorphone hydrochloride extended-release tablets and alcohol (240 mL of 20% or 4% alcohol).

The change in geometric mean C_{max} with concomitant administration of alcohol and hydromorphone hydrochloride extended-release tablets ranged from an increase of 10% to 31% across all conditions studied. The change in mean C_{max} was greater in the fasted group of subjects. Following concomitant administration of 240 mL of 40% alcohol while fasting, the mean C_{max} increased by 37% and up to 151% in an individual subject. Following the concomitant administration of 240 mL of 20% alcohol while fasting, the mean C_{max} increased by 35% and up to 139% in an individual subject. Following the concomitant administration of 240 mL of 4% alcohol while fasting, the mean C_{max} increased by 19% on average and as much as 73% for an individual subject. The range of median T_{max} for the fed and fasted treatments with 4%, 20% and 40% alcohol was 12 to 16 hours compared to 16 hours for the 0% alcohol treatments.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies to evaluate the carcinogenic potential of hydromorphone hydrochloride were completed in both Han-Wistar rats and Crl:CD1®(ICR) mice. Hydromorphone HCl was administered to Han-Wistar rats (2, 5, and 15 mg/kg/day for males, and 8, 25 and 75 mg/kg/day for females) for 2 years by oral gavage. In female rats, incidences of hibernoma (tumor of brown fat) were increased at 10.5 times the maximum recommended daily exposure based on AUC at the mid dose (2 tumor, 25 mg/kg/day) and 53.7 times the maximum recommended human daily exposure based on AUC at the maximum dose (4 tumors, 75 mg/kg/day). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in male rats. The systemic drug exposure (AUC, ng•h/mL) at the 15 mg/kg/day in male rats was 7.6 times greater than the human exposure at a single dose of 32 mg/day of hydromorphone hydrochloride extended-release tablets. There was no evidence of carcinogenic potential in Crl:CD1®(ICR) mice administered hydromorphone HCl at doses up to 15 mg/kg/day for 2 years by oral gavage. The systemic drug exposure (AUC, ng•h/mL) at the 15 mg/kg/day in mice was 1.1 (in males) and 1.2 (in females) times greater than the human exposure at a single dose of 32 mg/day of hydromorphone hydrochloride extended-release tablets.

Mutagenesis

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 (0.7, 1.4, or 2.8 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.

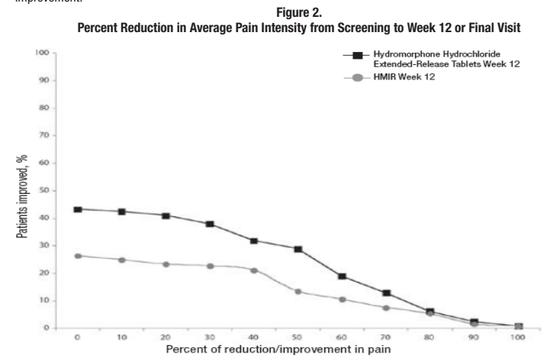
14 CLINICAL STUDIES

Hydromorphone hydrochloride extended-release tablets was investigated in a double-blind, placebo-controlled, randomized withdrawal study in opioid tolerant patients with moderate-to-severe low back pain. Patients were considered opioid tolerant if they were currently on opioid therapy that was ≥ 60 mg/day of oral morphine equivalent for at least 2 months prior to screening. Patients entered an open-label conversion and titration phase with hydromorphone hydrochloride extended-release tablets, were converted to a starting dose that was approximately 75% of their total daily morphine equivalent dose, and were dosed once daily until adequate pain control was achieved while exhibiting tolerable side effects. Supplemental immediate-release hydromorphone tablets were allowed throughout the study. Patients who achieved a stable dose entered a 12-week, double-blind, placebo-controlled, randomized treatment phase. Mean daily dose at randomization was 37.8 mg/day (range of 12 mg/day to 64 mg/day). Fifty-eight (58) percent of patients were successfully titrated to a stable dose of hydromorphone hydrochloride extended-release tablets during the open-label conversion and titration phase.

During the double-blind treatment phase, patients randomized to hydromorphone hydrochloride extended-release tablets continued with the stable dose achieved in the conversion and titration phase of the study. Patients randomized to placebo received, in a blinded manner, hydromorphone hydrochloride extended-release tablets and matching placebo in doses tapering from the stable dose achieved in conversion and titration. During the taper down period, patients were allowed immediate-release hydromorphone tablets as supplemental analgesia to minimize opioid withdrawal symptoms in placebo patients. After the taper period, the number of immediate-release hydromorphone tablets was limited to two tablets per day. Forty-nine (49) percent of patients treated with hydromorphone hydrochloride extended-release tablets and 33% of patients treated with placebo completed the 12-week treatment period.

Hydromorphone hydrochloride extended-release tablets provided superior analgesia compared to placebo. There was a significant difference between the mean changes from Baseline to Week 12 or Final Visit in average weekly pain intensity Numeric Rating Scale (NRS) scores obtained from patient diaries between the two groups. The proportion of patients with various degrees of improvement from screening to Week 12 or Final Visit is shown in **Figure 2**. For this analysis, patients who discontinued treatment for any reason prior to Week 12 were assigned a value of zero improvement.

Figure 2.
Percent Reduction in Average Pain Intensity from Screening to Week 12 or Final Visit



16 HOW SUPPLIED/STORAGE AND HANDLING

Hydromorphone Hydrochloride Extended-Release Tablet Strengths

The 8 mg tablets are Light pink to pink film coated, round, biconvex tablets printed with "266" in black ink on one side of the tablet

NDC 31722-119-01 bottles of 100 tablets

The 12 mg tablets are Light yellow to yellow film coated, round, biconvex tablets printed with "267" in black ink on one side of the tablet

NDC 31722-120-01 bottles of 100 tablets

The 16 mg tablets are Light beige to beige film coated, round, biconvex tablets printed with "268" in black ink on one side of the tablet

NDC 31722-121-01 bottles of 100 tablets

The 32 mg tablets are White to off white film coated, round, biconvex tablets printed with "269" with black ink on one side of the tablet

NDC 31722-122-01 bottles of 100 tablets

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature].

Store hydromorphone hydrochloride extended-release tablets securely and dispose of properly *[see Patient Counseling Information (17)]*.

17 PATIENT COUNSELING INFORMATION

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

Storage and Disposal

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store hydromor