HYDROMORPHONE HYDROCHLORIDE- hydromorphone hydrochloride tablet, extended release
Padagis US LLC

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 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. (5.1)
• 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

Boxed Warning	11/2023
Indications and Usage (1)	11/2023
Dosage and Administration (2.1, 2.3, 2.4)	01/2024
Warnings and Precautions (5.6)	11/2023

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 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 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 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 the 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 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 (OIH) 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, 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 Padagis® at 1-866-634-9120 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.

Revised: 1/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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. Instruct patients to swallow hydromorphone hydrochloride extended-release tablets whole; crushing, chewing, or dissolving hydromorphone hydrochloride extended-release tablets can cause rapid release and absorption of a potentially fatal dose of hydromorphone *[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 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 Information

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 tablet 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 tablet 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 a hydromorphone hydrochloride extended-release tablet 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 is 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 tablet 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 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 dose 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: round, biconvex, dark beige tablets imprinted with “P293” over “8” on one side.

12 mg tablets: round, biconvex, white tablets imprinted with “P294” over “12” on one side.

16 mg tablets: round, biconvex, light beige tablets imprinted with “P295” over “16” on one side.

32 mg tablets: round, biconvex, pink tablets imprinted with "P297" over "32" on one side.

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 contain hydromorphone, a Schedule II controlled substance. As an opioid, hydromorphone hydrochloride extended-release tablets expose 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 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), Overdosage (10), Patient Counseling Information (17)].*

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 emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

Advise both patients and caregivers about the risks of respiratory depression and sedation when hydromorphone hydrochloride extended-release 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)]*.

5.4 Neonatal Opioid Withdrawal Syndrome

Use of hydromorphone hydrochloride extended-release tablets for an extended period of time during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)].*

5.5 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

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. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the

Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

5.6 Opioid-Induced Hyperalgesia and Allodynia

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

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation (safely switching the patient to a different opioid moiety) *[see Dosage and Administration (2.5); Warnings and Precautions (5.13)]*.

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

The use of hydromorphone hydrochloride extended-release 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 extended-release tablets 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 extended-release tablets *[see Warnings and Precautions (5.2)]*.

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 (5.2)]*.

Regularly evaluate such patients closely, particularly when initiating and titrating hydromorphone hydrochloride extended-release tablets and when hydromorphone hydrochloride extended-release tablets are given concomitantly with other drugs that

depress respiration *[see Warnings and Precautions (5), Drug Interactions (7)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.8 Adrenal Insufficiency

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

5.9 Severe Hypotension

Hydromorphone hydrochloride extended-release tablets may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an 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)]*. Regularly evaluate these patients for signs of hypotension after initiating or titrating the dosage of hydromorphone hydrochloride extended-release tablets. In patients with circulatory shock, hydromorphone hydrochloride extended-release tablets may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of hydromorphone hydrochloride extended-release tablets in patients with circulatory shock.

5.10 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 extended-release 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 extended-release tablets.

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

5.11 Risks of Use in Patients with Gastrointestinal Conditions

Hydromorphone hydrochloride extended-release tablets are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. Avoid the use of hydromorphone hydrochloride extended-release tablets in patients with other GI obstruction.

Because the shell of the hydromorphone hydrochloride extended-release tablet is

insoluble, it may remain intact during gastrointestinal transit and be eliminated in the feces. Hydromorphone hydrochloride extended-release tablets are contraindicated in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, “short gut” syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel’s diverticulum). There have been reports of obstructive symptoms in patients with known strictures or risk of strictures, such as previous GI surgery, in association with the ingestion of drugs in nondeformable extended-release formulations.

It is possible that hydromorphone hydrochloride extended-release tablets may be visible on abdominal x-rays under certain circumstances, especially when digital enhancing techniques are utilized.

The hydromorphone in hydromorphone hydrochloride extended-release tablets may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Regularly evaluate patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.12 Increased Risk of Seizures in Patients with Seizure Disorders

The hydromorphone in hydromorphone hydrochloride extended-release 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. Regularly evaluate patients with a history of seizure disorders for worsened seizure control during hydromorphone hydrochloride extended-release tablet therapy.

5.13 Withdrawal

Do not abruptly discontinue hydromorphone hydrochloride extended-release tablets in a patient physically dependent on opioids. When discontinuing hydromorphone hydrochloride extended-release tablets in a physically dependent patient, gradually taper the dosage. Rapid tapering of hydromorphone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain *[see Dosage and Administration (2.5), Drug Abuse and Dependence (9.3)]*.

Additionally, 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 extended-release tablets. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms *[see Drug Interactions (7)]*.

5.14 Sulfites

Hydromorphone hydrochloride extended-release 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 *[see Adverse Reactions (6.2)]*.

5.15 Risks of Driving and Operating Machinery

Hydromorphone hydrochloride extended-release tablets may impair the mental and/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 extended-release tablets and know how they will react to the medication *[see Patient Counseling Information (17)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Interactions with Benzodiazepine or Other CNS Depressants *[see Warnings and Precautions (5.3)]*
- Opioid-Induced Hyperalgesia and Allodynia *[see Warnings and Precautions (5.6)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.8)]*
- Severe Hypotension *[see Warnings and Precautions (5.9)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.11)]*
- Seizures *[see Warnings and Precautions (5.12)]*
- Withdrawal *[see Warnings and Precautions (5.13)]*

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.

Hydromorphone hydrochloride extended-release tablets were administered to a total of 2,524 patients in 15 controlled and uncontrolled clinical studies. Of these, 423 patients were exposed to hydromorphone hydrochloride extended-release tablets for greater than 6 months and 141 exposed for greater than one year.

The most common adverse reactions leading to study discontinuation were nausea, vomiting, constipation, somnolence, and dizziness. The most common treatment-related serious adverse reactions from controlled and uncontrolled chronic pain studies were drug withdrawal syndrome, overdose, confusional state, and constipation.

The overall incidence of adverse reactions in patients greater than 65 years of age was higher, with a greater than 5% difference in rates for constipation and nausea when compared with younger patients. The overall incidence of adverse reactions in female patients was higher, with a greater than 5% difference in rates for nausea, vomiting, constipation and somnolence when compared with male patients.

A 12-week double-blind, placebo-controlled, randomized withdrawal study was conducted in opioid tolerant patients with moderate to severe low back pain *[see Clinical Studies (14)]*. A total of 447 patients were enrolled into the open-label titration phase with 268 patients randomized into the double-blind treatment phase. The adverse reactions that were reported in at least 2% of the patients are contained in **Table 2**.

Table 2.

Number (%) of Patients with Adverse Reactions Reported in ≥ 2% of Patients with Moderate to Severe Low Back Pain During the Open-Label Titration Phase or Double-Blind Treatment Phase by Preferred Term

Preferred Term	Open-Label Titration Phase Hydromorphone Hydrochloride Extended-Release Tablets (N=447)	Double-Blind Treatment Phase	
		Hydromorphone Hydrochloride Extended-Release Tablets (N=134)	Placebo (N=134)
Constipation	69 (15)	10 (7)	5 (4)
Nausea	53 (12)	12 (9)	10 (7)
Somnolence	39 (9)	1 (1)	0 (0)
Headache	35 (8)	7 (5)	10 (7)
Vomiting	29 (6)	8 (6)	6 (4)
Pruritus	21 (5)	1 (1)	0 (0)
Dizziness	17 (4)	3 (2)	2 (1)
Insomnia	13 (3)	7 (5)	5 (4)
Dry Mouth	13 (3)	2 (1)	0 (0)
Edema Peripheral	13 (3)	3 (2)	1 (1)
Hyperhidrosis	13 (3)	2 (1)	2 (1)
Anorexia/Decreased Appetite	10 (2)	2 (1)	0 (0)
Arthralgia	9 (2)	8 (6)	3 (2)
Abdominal Pain	9 (2)	4 (3)	3 (2)
Muscle Spasms	5 (1)	3 (2)	1 (1)
Weight Decreased	3 (1)	4 (3)	3 (2)

The adverse reactions that were reported in at least 2% of the total treated patients (N=2,474) in the 14 chronic clinical trials are contained in **Table 3**.

Table 3.

Number (%) of Patients with Adverse Reactions Reported in ≥ 2% of Patients with Chronic Pain Receiving Hydromorphone Hydrochloride Extended-Release Tablets in 14 Clinical Studies by Preferred Term

Preferred Term	All Patients (N=2,474)
Constipation	765 (31)
Nausea	684 (28)
Vomiting	337 (14)
Somnolence	367 (15)
Headache	308 (12)
Asthenia/Fatigue	272 (11)
Dizziness	262 (11)
Diarrhea	201 (8)
Pruritus	193 (8)

Insomnia	161 (7)
Hyperhidrosis	143 (6)
Edema Peripheral	135 (5)
Anorexia/Decreased Appetite	139 (6)
Dry Mouth	121 (5)
Abdominal Pain	115 (5)
Anxiety	95 (4)
Back Pain	95 (4)
Dyspepsia*	88 (4)
Depression	81 (3)
Dyspnea	76 (3)
Muscle Spasms	74 (3)
Arthralgia	72 (3)
Rash	64 (3)
Pain in Extremity	63 (3)
Pain	58 (2)
Drug Withdrawal Syndrome	55 (2)
Pyrexia	52 (2)
Fall	51 (2)
Chest Pain	51 (2)

* Reflux esophagitis, gastroesophageal reflux disease and Barrett's esophagus were grouped and reported with dyspepsia

The following Adverse Reactions occurred in patients with an overall frequency of <2% and are listed in descending order within each System Organ Class:

Cardiac disorders: palpitations, tachycardia, bradycardia, extrasystoles

Ear and labyrinth disorders: vertigo, tinnitus

Endocrine disorders: hypogonadism

Eye disorders: vision blurred, diplopia, dry eye, miosis

Gastrointestinal disorders: flatulence, dysphagia, hematochezia, abdominal distension, hemorrhoids, abnormal feces, intestinal obstruction, eructation, diverticulum, gastrointestinal motility disorder, large intestine perforation, anal fissure, bezoar, duodenitis, ileus, impaired gastric emptying, painful defecation

General disorders and administration site conditions: chills, malaise, feeling abnormal, feeling of body temperature change, feeling jittery, hangover, gait disturbance, feeling drunk, body temperature decreased

Infections and infestations: gastroenteritis, diverticulitis

Injury, poisoning and procedural complications: contusion, overdose

Investigations: weight decreased, hepatic enzyme increased, blood potassium decreased, blood amylase increased, blood testosterone decreased

Metabolism and nutrition disorders: dehydration, fluid retention, increased appetite, hyperuricemia

Musculoskeletal and connective tissue disorders: myalgia

Nervous system disorders: tremor, sedation, hypoesthesia, paresthesia, disturbance in attention, memory impairment, dysarthria, syncope, balance disorder, dysgeusia, depressed level of consciousness, coordination abnormal, hyperesthesia, myoclonus, dyskinesia, crying, hyperreflexia, encephalopathy, cognitive disorder, convulsion, psychomotor hyperactivity

Psychiatric disorders: confusional state, nervousness, restlessness, abnormal dreams, mood altered, hallucination, panic attack, euphoric mood, paranoia, dysphoria, listless, suicide ideation, libido decreased, aggression

Renal and urinary disorders: dysuria, urinary retention, urinary frequency, urinary hesitation, micturition disorder

Reproductive system and breast disorders: erectile dysfunction, sexual dysfunction

Respiratory, thoracic and mediastinal disorders: rhinorrhea, respiratory distress, hypoxia, bronchospasm, sneezing, hyperventilation, respiratory depression

Skin and subcutaneous tissue disorders: erythema

Vascular disorders: flushing, hypertension, hypotension

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.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs *[see Drug Interactions (7)].*

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use *[see Warnings and Precautions (5.8)].*

Anaphylaxis: Anaphylactic reaction has been reported with ingredients contained in hydromorphone hydrochloride extended-release tablets *[see Contraindications (4) and Warnings and Precautions (5.14)].*

Androgen deficiency: Cases of androgen deficiency have occurred with use of opioids for an extended period of time *[see Clinical Pharmacology (12.2)].*

Hyperalgesia and Allodynia: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration *[see Warnings and Precautions (5.6)].*

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g. diabetes).

7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with hydromorphone hydrochloride extended-release tablets.

Table 4. Clinically Significant Drug Interactions with Hydromorphone Hydrochloride Extended-Release 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. 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 Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.2, 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, frequently evaluate the patient, particularly during treatment initiation and dose adjustment. Discontinue hydromorphone hydrochloride extended-release 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), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.3)].*
Intervention:	The use of hydromorphone hydrochloride extended-release 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 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 skeletal muscle relaxants and opioids, consider prescribing naloxone for the emergency treatment of opioid overdose *[see Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.3)]*.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Evaluate 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:	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. Regularly evaluate 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. Regularly evaluate 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 contain hydromorphone, a Schedule II controlled substance.

9.2 Abuse

Hydromorphone hydrochloride extended-release tablets contain 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. This risk is increased with concurrent use of hydromorphone hydrochloride extended-release tablets with alcohol and/or other CNS depressants. Taking cut, broken, chewed, crushed, or

dissolved hydromorphone hydrochloride extended-release tablets enhances drug release and increases the risk of overdose and death.

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 disease 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),*

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 overdosage 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 re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen, 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 hydromorphone 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.

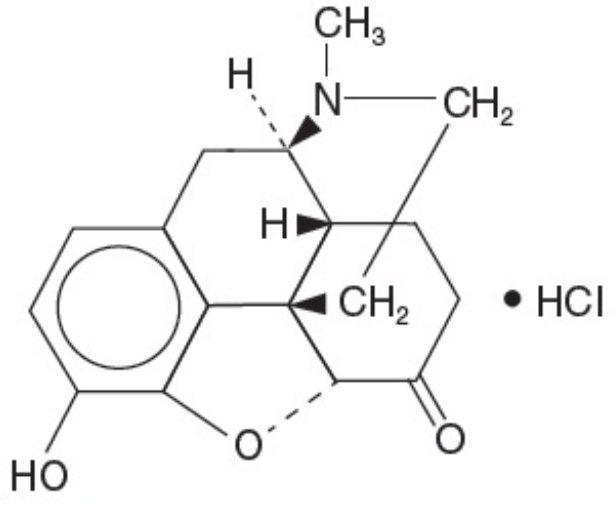
In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. 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 contain the following inactive ingredients: ammonio methacrylate copolymer, colloidal silicon dioxide, ethylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, povidone, talc and triethyl citrate.

The color coating of the tablets contains FD&C Blue No. 1, ferric oxide red (8, 16, and 32 mg only), ferric oxide yellow (8 and 16 mg only), hypromellose, polyethylene glycol, polysorbate 80 (12 mg only), propylene glycol, and titanium dioxide.

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

Figure 1.
Mean Steady-State Plasma Concentration Profile

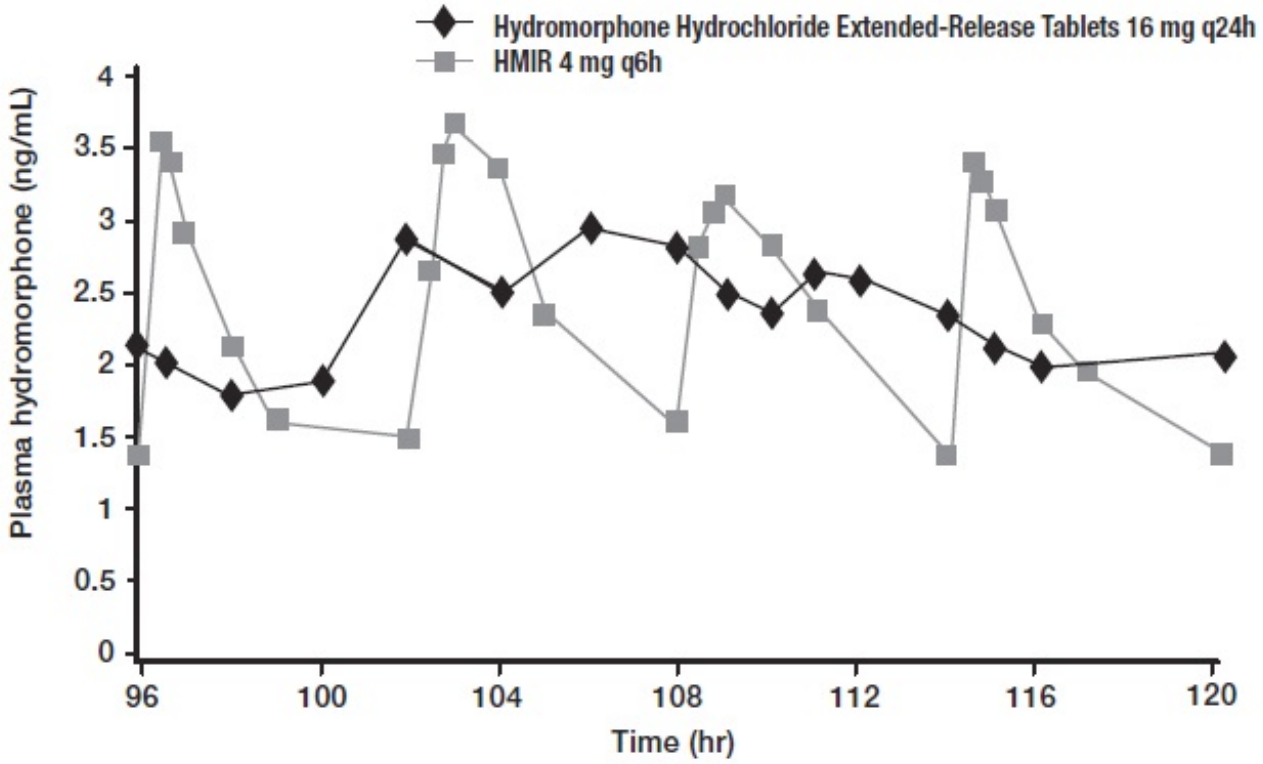


Table 5.

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

Regimen	Dosage	T_{max}* (hrs)	C_{max} (ng/mL)	AUC (ng●hr/mL)	$T_{1/2}$ (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 were 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.

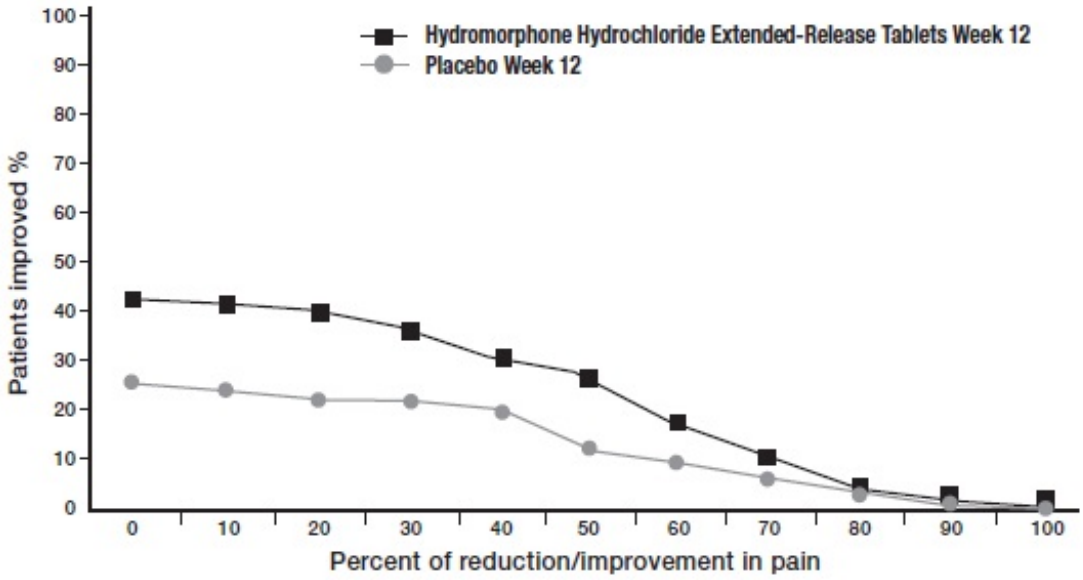
During the double-blind treatment phase, patients randomized to hydromorphone

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				
Strength	**Color**	**Tablet Description**	**Bottle Count**	**NDC**
8 mg	**Dark Beige**	Round, biconvex, imprinted with “P293” over “8” on one side	**100**	0574-0293-01
12 mg	**White**	Round, biconvex, imprinted with “P294” over “12” on one side	**100**	0574-0294-01

16 mg	**Light Beige**	Round, biconvex, imprinted with “P295” over “16” on one side	**100**	0574-0295-01
32 mg	**Pink**	Round, biconvex, imprinted with “P297” over “32” on one side	**100**	0574-0297-01

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 hydromorphone hydrochloride extended-release tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home. Inform patients that leaving hydromorphone hydrochloride extended-release tablets unsecured can pose a deadly risk to others in the home *[see Warnings and Precautions (5.1, 5.5), Drug Abuse and Dependence (9.2)]*.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Expired, unwanted, or unused hydromorphone hydrochloride extended-release tablets should be disposed of by flushing the unused medication down the toilet if a drug take-back option is not readily available. Inform patients that they can visit www.fda.gov/drugdisposal for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines.

Addiction, Abuse, and Misuse

Inform patients that the use of hydromorphone hydrochloride extended-release tablets, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share hydromorphone hydrochloride extended-release tablets with others and to take steps to protect hydromorphone hydrochloride extended-release 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 extended-release tablets or when the dose is increased, and that it can occur even at recommended dosages.

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 Warnings and Precautions (5.2)]*.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if hydromorphone hydrochloride extended-release tablets are used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Discuss with the patient and caregiver the availability of naloxone for the emergency treatment of opioid overdose, 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) *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.

Explain to patients and caregivers that naloxone's effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered *[see Overdosage (10)]*.

If naloxone is prescribed, also advise patients and caregivers:

- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone and to keep it in a place where family and friends can access it in an emergency
- To read the Patient Information (or other educational material) that will come with their naloxone. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Hyperalgesia and Allodynia

Inform patients and caregivers not to increase opioid dosage without first consulting a clinician. Advise patients to seek medical attention if they experience symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain *[see Warnings and Precautions (5.6); Adverse Reactions (6.2)]*.

Serotonin Syndrome

Inform patients that hydromorphone hydrochloride extended-release 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 extended-release tablets while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking hydromorphone hydrochloride extended-release tablets *[see Drug*

Interactions (7)].

Important Administration Instructions

Instruct patients how to properly take hydromorphone hydrochloride extended-release tablets, including the following:

- Hydromorphone hydrochloride extended-release tablets are designed to work properly only if swallowed intact. Taking cut, broken, chewed, crushed, or dissolved hydromorphone hydrochloride extended-release tablets can result in a fatal overdose *[see Dosage and Administration (2.1)]*.

- Using hydromorphone hydrochloride extended-release tablets exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression)

Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue hydromorphone hydrochloride extended-release tablets without first discussing a tapering plan with the prescriber *[see Dosage and Administration (2.5)]*.

Driving or Operating Heavy Machinery

Inform patients that hydromorphone hydrochloride extended-release 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 (5.15)]*.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2)]*.

Adrenal Insufficiency

Inform patients that hydromorphone hydrochloride extended-release tablets 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 (5.8)]*.

Gastrointestinal Blockage

Advise patients that people with certain stomach or intestinal problems such as narrowing of the intestines or previous surgery may be at higher risk of developing a blockage. Symptoms include abdominal distension, abdominal pain, severe constipation, or vomiting. Instruct patients to contact their healthcare provider immediately if they develop these symptoms.

Hypotension

Inform patients that hydromorphone hydrochloride extended-release 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).

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in hydromorphone hydrochloride extended-release tablets. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Warnings and Precautions (5.14), and Adverse Reactions (6.2)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that use of hydromorphone hydrochloride extended-release tablets for an extended period of time 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 extended-release tablets can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that breastfeeding is not recommended during treatment with hydromorphone hydrochloride extended-release tablets *[see Use in Specific Populations (8.2)].*

Infertility

Inform patients that use of opioids for an extended period of time may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Manufactured by Padagis

Minneapolis, MN 55427

www.padagis.com

Rev 01-24
1B500 RC PH18
2204851

PHARMACIST: Dispense a separate Medication Guide to each patient. Dispense with Medication Guide available at www.padagis.com/medguide/HDMRTabs

Medication Guide

Dispense with Medication Guide available at www.padagis.com/medguide/HDMRTabs

Medication Guide

Hydromorphone Hydrochloride (hy-dr*uh*-mor-fon hy-dr*uh*-klawr-ahyd) Extended-Release Tablets, CII

Hydromorphone hydrochloride extended-release tablets are:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine when other pain medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine 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.
- Not to be taken on an “as needed” basis.

Important information about hydromorphone hydrochloride extended-release tablets:

- **Get emergency help or call 911 right away if you take too many hydromorphone hydrochloride extended-release tablets (overdose).** When you first start taking hydromorphone hydrochloride extended-release 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. Talk to your healthcare provider about naloxone, a medicine for the emergency treatment of an opioid overdose.
- Taking hydromorphone hydrochloride extended-release 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 extended-release tablets. They could die from taking it. Selling or giving away hydromorphone hydrochloride extended-release tablets is against the law.
- Store hydromorphone hydrochloride extended-release tablets securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

Do not take hydromorphone hydrochloride extended-release 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 extended-release tablets, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- allergy to sulfites
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental

health problems.

Tell your healthcare provider if you:

- notice your pain getting worse. If your pain gets worse after you take hydromorphone hydrochloride extended-release tablets, do not take more of hydromorphone hydrochloride extended-release tablets without first talking to your healthcare provider. Talk to your healthcare provider if the pain that you have increases, if you feel more sensitive to pain, or if you have new pain after taking hydromorphone hydrochloride extended-release tablets.
- **are pregnant or planning to become pregnant.** Use of hydromorphone hydrochloride extended-release tablets for an extended period of time during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **are breastfeeding.** Not recommended during treatment with hydromorphone hydrochloride extended-release tablets. It may harm your baby.
- are living in a household where there are small children or someone who has abused street or prescription drugs.
- are taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking hydromorphone hydrochloride extended-release tablets with certain other medicines can cause serious side effects.

When taking hydromorphone hydrochloride extended-release tablets:

- Do not change your dose. Take hydromorphone hydrochloride extended-release tablets exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 24 hours, at the same time every day. Do not take more than your prescribed dose in 24 hours. If you miss a dose, take your next dose at your usual time the next day.
- Swallow hydromorphone hydrochloride extended-release tablets whole. Do not cut, break, chew, crush, dissolve, snort, or inject hydromorphone hydrochloride extended-release tablets because this may cause you to overdose and die.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking hydromorphone hydrochloride extended-release tablets without talking to your healthcare provider.**
- Hydromorphone hydrochloride extended-release tablets are contained in a hard tablet shell that you may see in your bowel movement; this is normal.
- Dispose of expired, unwanted, or unused hydromorphone hydrochloride extended-release tablets by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

While taking hydromorphone hydrochloride extended-release tablets, DO NOT:

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

The possible side effects of hydromorphone hydrochloride extended-release tablets are:

- 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 or call 911 right away 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 extended-release tablets. Call your healthcare provider 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 Padagis, Minneapolis, MN 55427

1B500 RC MG8

www.padagis.com or call 1-866-634-9120

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

Revised September 2023

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – 8 mg

NDC 0574-0293-01

Rx Only

Once Daily

HYDROmorphone HCl Extended-Release Tablets 8 mg

CII

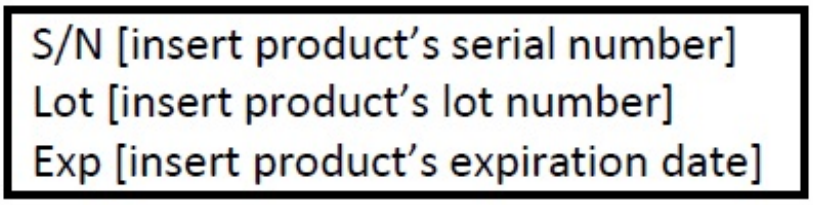
For opioid tolerant patients only

Dispense the accompanying Medication Guide to each patient. Print Medication Guides at

www.padagis.com/medguide/HDMRTabs

100 TABLETS

The following image is a placeholder representing the product identifier that is either affixed or imprinted on the drug package label during the packaging operation.



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – 12 mg

0574-0294-01

Rx Only

Once Daily

HYDROmorphone HCl Extended-Release Tablets 12 mg

CII

For opioid tolerant patients only

Dispense the accompanying Medication Guide to each patient. Print Medication Guides at www.padagis.com/medguide/HDMRTabs

100 TABLETS

The following image is a placeholder representing the product identifier that is either affixed or imprinted on the drug package label during the packaging operation.

S/N [insert product's serial number]
Lot [insert product's lot number]
Exp [insert product's expiration date]

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – 16 mg

NDC 0574-0295-01

Rx Only

Once Daily

HYDROmorphone HCl Extended-Release Tablets 16 mg

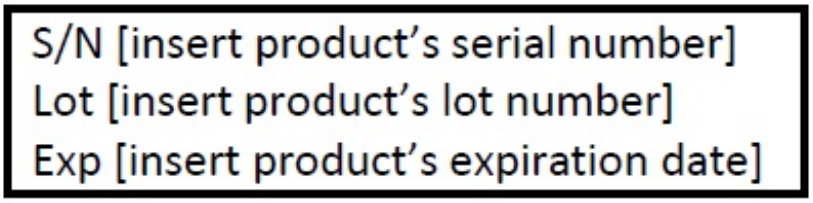
CII

For opioid tolerant patients only

Dispense the accompanying Medication Guide to each patient. Print Medication Guides at www.padagis.com/medguide/HDMRTabs

100 TABLETS

The following image is a placeholder representing the product identifier that is either affixed or imprinted on the drug package label during the packaging operation.



Package/Label Display Panel – 32 mg

NDC 0574-0297-01

Rx Only

Once Daily

HYDROmorphone HCl Extended-Release Tablets 32 mg

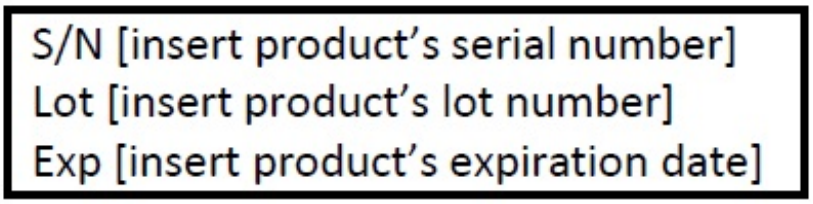
CII

For opioid tolerant patients only

Dispense the accompanying Medication Guide to each patient. Print Medication Guides at www.padagis.com/medguide/HDMRTabs

100 TABLETS

The following image is a placeholder representing the product identifier that is either affixed or imprinted on the drug package label during the packaging operation.



HYDROMORPHONE HYDROCHLORIDE

hydromorphone hydrochloride tablet, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0574-0293
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HYDROMORPHONE HYDROCHLORIDE (UNII: L960UP2KRW) (HYDROMORPHONE - UNII:Q812464R06)	HYDROMORPHONE HYDROCHLORIDE	8 mg

Inactive Ingredients	
Ingredient Name	**Strength**
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
MANNITOL (UNII: 3OWL53L36A)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
ETHYLCELLULOSE (100 MPA.S) (UNII: 47MLB0F1MV)	
POVIDONE K30 (UNII: U725QWY32X)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	

AMMONIO METHACRYLATE COPOLYMER TYPE A (UNII: 8GQS4E66YY)	
TALC (UNII: 7SEV7J4R1U)	
HYPROMELLOSE 2910 (3 MPA.S) (UNII: 0VUT3PMY82)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics

Color	BROWN (Dark Beige)	**Score**	no score
Shape	ROUND (biconvex)	**Size**	7mm
Flavor		**Imprint Code**	P293;8
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0574-0293-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	05/22/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204278	05/22/2015	

HYDROMORPHONE HYDROCHLORIDE

hydromorphone hydrochloride tablet, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0574-0294
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HYDROMORPHONE HYDROCHLORIDE (UNII: L960UP2KRW) (HYDROMORPHONE - UNII:Q812464R06)	HYDROMORPHONE HYDROCHLORIDE	12 mg

Inactive Ingredients

Ingredient Name	Strength

MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
MANNITOL (UNII: 3OWL53L36A)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
ETHYLCELLULOSE (100 MPA.S) (UNII: 47MLB0F1MV)	
POVIDONE K30 (UNII: U725QWY32X)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
AMMONIO METHACRYLATE COPOLYMER TYPE A (UNII: 8GQS4E66YY)	
TALC (UNII: 7SEV7J4R1U)	
HYPROMELLOSE 2910 (3 MPA.S) (UNII: 0VUT3PMY82)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	

Product Characteristics

Color	WHITE	**Score**	no score
Shape	ROUND (biconvex)	**Size**	8mm
Flavor		**Imprint Code**	P294;12
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0574-0294-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	05/22/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204278	05/22/2015	

HYDROMORPHONE HYDROCHLORIDE

hydromorphone hydrochloride tablet, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0574-0295
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HYDROMORPHONE HYDROCHLORIDE (UNII: L960UP2KRW) (HYDROMORPHONE - UNII:Q812464R06)	HYDROMORPHONE HYDROCHLORIDE	16 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
MANNITOL (UNII: 3OWL53L36A)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
ETHYLCELLULOSE (100 MPA.S) (UNII: 47MLB0F1MV)	
POVIDONE K30 (UNII: U725QWY32X)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
AMMONIO METHACRYLATE COPOLYMER TYPE A (UNII: 8GQS4E66YY)	
TALC (UNII: 7SEV7J4R1U)	
HYPROMELLOSE 2910 (3 MPA.S) (UNII: 0VUT3PMY82)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics

Color	BROWN (Light Beige)	**Score**	no score
Shape	ROUND (biconvex)	**Size**	9mm
Flavor		**Imprint Code**	P295;16
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0574-0295-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	05/22/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204278	05/22/2015	

HYDROMORPHONE HYDROCHLORIDE

hydromorphone hydrochloride tablet, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0574-0297
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HYDROMORPHONE HYDROCHLORIDE (UNII: L960UP2KRW) (HYDROMORPHONE - UNII:Q812464R06)	HYDROMORPHONE HYDROCHLORIDE	32 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
MANNITOL (UNII: 3OWL53L36A)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
ETHYLCELLULOSE (100 MPA.S) (UNII: 47MLB0F1MV)	
POVIDONE K30 (UNII: U725QWY32X)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
AMMONIO METHACRYLATE COPOLYMER TYPE A (UNII: 8GQS4E66YY)	
TALC (UNII: 7SEV7J4R1U)	
HYPROMELLOSE 2910 (3 MPA.S) (UNII: 0VUT3PMY82)	
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics

Color	PINK	**Score**	no score
Shape	ROUND (biconvex)	**Size**	9mm
Flavor		**Imprint Code**	P297;32
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0574-0297-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	09/29/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

ANDA	ANDA204278	05/22/2015	

Labeler - Padagis US LLC (967694121)

Revised: 1/2024 Padagis US LLC