HYDROMORPHONE HYDROCHLORIDE—hydromorphone hydrochloride tablet, film coated, extended release
Actavis Pharma, Inc.

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 HCL extended-release tablets, for oral use, CII
Initial U.S. Approval: 1984

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

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).
- 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 (5.3).
- 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 (5.4, 7).

RECENT MAJOR CHANGES

- INDICATIONS AND USAGE

Hydromorphone hydrochloride extended-release tablets are an opioid agonist indicated in opioid-tolerant patients for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (1).

Patients considered opioid tolerant are those who are taking, for one week or longer, at least 60 mg oral morphine per day, 25 mg transdermal fentanyl per day, 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 (1).

Limitations of Use (1)

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, 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.
- Hydromorphone hydrochloride extended-release tablets are not indicated as an as-needed (prn) analgesic.

DOSEAGE AND ADMINISTRATION

To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain. (1)

For once daily administration in opioid-tolerant patients (2.1).

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).

Individualize dosing based on the severity of pain, patients response, prior analgesic experience, and risk factors for addiction, abuse, and misuse (2.1).

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).

Do not abruptly discontinue hydromorphone hydrochloride extended-release tablets in a physically-dependent patient (2.1).

To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain.

CONTRAINICATIONS

- Opioid non-tolerant patients (4)
- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in the presence of respiratory depression (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, 5.12)

WARNINGS AND PRECAUTIONS

Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or Elderly, Cachectic, Debilitated Patients: Monitor closely, particularly during initiation and titration (5.5).

Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid (5.5).

Severe Hypotension: Monitor during dose initiation and titration. Avoid use of hydromorphone hydrochloride extended-release tablets in patients with circulatory shock (5.7).

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 (5.8).

ADVERSE REACTIONS

Most common adverse reactions (incidence greater than 10%) are: constipation, nausea, vomiting, somnolence, headache, and dizziness (6.1).
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 (5.11, 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.

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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1 INDICATIONS AND USAGE

Hydromorphone hydrochloride extended-release tablets are indicated for the management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment 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 mg 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 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, or an equianalgesic dose of another opioid.

Limitations of Use

- Because of the risk of addiction, abuse, and misuse with opioids, even at recommended doses, 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.
- 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 in the use of potent opioids for the management of chronic pain.

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

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

- Use the lowest effective dosage for the shortest duration consistent with individual patient...
treatment goals [see Warnings and Precautions (5)].

- Initiate the dosing regimen for each patient individually, taking into account the patient’s prior analgesic treatment experience and risk factors for addiction, abuse, and misuse [see Warnings and Precautions (5.1)].

- Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with hydromorphone hydrochloride extended-release tablets and adjust the dosage accordingly [see Warnings and Precautions (5.2)].

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 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

Discontinue all other around-the-clock opioid drugs when hydromorphone hydrochloride extended-release tablets therapy is initiated.

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 than to overestimate the 24-hour oral hydromorphone dosage and manage an adverse reaction due to overdose.

In a hydromorphone hydrochloride extended-release tablets clinical trial with an open-label titration period, patients were converted from their prior opioid to hydromorphone hydrochloride extended-release tablets using the Table 1 as a guide for the initial hydromorphone hydrochloride extended-release tablets dose. The recommended starting dose of hydromorphone hydrochloride extended-release tablets 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

<table>
<thead>
<tr>
<th>Prior Oral Opioid</th>
<th>Approximate Oral Conversion Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone</td>
<td>1</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.06</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>0.4</td>
</tr>
<tr>
<td>Methadone</td>
<td>0.6</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.2</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>0.4</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>0.6</td>
</tr>
</tbody>
</table>

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

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

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

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

**Step 1:** Sum the total daily dose of the opioid

- 30 mg of oxycodone 2 times daily = 60 mg total daily dose of oxycodone

**Step 2:** Calculate the approximate equivalent dose of oral hydromorphone based on the total daily dose of the current opioid using Table 1

- 60 mg total daily dose of oxycodone x Conversion Factor of 0.4 = 24 mg of oral hydromorphone daily

**Step 3:** Calculate the approximate starting dose of hydromorphone hydrochloride extended-release tablets to be given every 24 hours, which is 50% of the calculated oral hydromorphone dose. Round down, if necessary, to the appropriate hydromorphone hydrochloride extended-release tablets strength(s) available.

- 50% of 24 mg results in an initial dose of 12 mg of hydromorphone hydrochloride extended-release tablets 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.

2.3 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 and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse. 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 chronic therapy, 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 unacceptable opioid-related adverse reactions are observed, the subsequent doses may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.4 Discontinuation of Hydromorphone Hydrochloride Extended-Release Tablets

When a patient no longer requires therapy with hydromorphone hydrochloride extended-release tablets, taper doses gradually, by 25% to 50% every 2 to 3 days while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue hydromorphone hydrochloride extended-release tablets.

To dispose of unused hydromorphone hydrochloride extended-release tablets flush all remaining tablets down the toilet or remit to authorities at a certified drug take-back program.

2.5 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)].

2.6 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 is 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)].
Hydromorphone hydrochloride extended-release tablets are available in 8 mg, 12 mg, 16 mg, and 32 mg dosage strengths. The 8 mg tablets are reddish brown, round, film-coated tablets with black imprint stating “WPI” and “3629” on one side and plain on the other side. The 12 mg tablets are dark yellow, round, film-coated tablets with black imprint stating “WPI” and “3739” on one side and plain on the other side. The 16 mg tablets are beige to light yellow, round, film-coated tablets with black imprint stating “WPI” and “3630” on one side and plain on the other side. The 32 mg tablets are white to off-white, round, film-coated tablets with black imprint stating “WPI” and “3631” on one side and plain on the other side.

4 CONTRAINdications

Hydromorphone hydrochloride extended-release tablets are contraindicated in:
- 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 (5.5)).
- Known or suspected gastrointestinal obstruction, including paralytic ileus (see Warnings and Precautions (5.9)).
- 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 (5.9)).
- Patients with hypersensitivity (e.g., anaphylaxis) to hydromorphone (see Warnings and Precautions (5.12)).

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

Hydromorphone hydrochloride contains hydromorphone, a Schedule II controlled substance. As an opioid, hydromorphone hydrochloride exposes users to the risks of addiction, abuse, and misuse (see Drug Abuse and Dependence (9)). As modified-release products such as hydromorphone hydrochloride 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 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, and monitor all patients receiving hydromorphone hydrochloride 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 for the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations such as hydromorphone hydrochloride, but use in such patients necessitates intensive counseling about the risks and proper use of hydromorphone hydrochloride along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of hydromorphone hydrochloride 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 by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing hydromorphone hydrochloride. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug (see Patient Counseling Information (17)). Contact 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 (CO₂) 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, the risk is greatest during the initiation of therapy or following a dosage increase. Closely monitor patients for respiratory depression, especially within the first 24-72 hours of initiating therapy with hydromorphone hydrochloride and following dosage increases.

To reduce the risk of respiratory depression, proper dosing and titration of hydromorphone hydrochloride are essential (see Dosage and Administration (2)). Overestimating the hydromorphone hydrochloride 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, especially by children, can result in respiratory depression and death due to an overdose of hydromorphone.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of hydromorphone hydrochloride during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (see
5.4 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 with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antidepressants, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

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

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosage and minimum duration of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

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

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

The use of hydromorphone hydrochloride 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 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 [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)].

Monitor such patients closely, particularly when initiating or titrating hydromorphone hydrochloride and when hydromorphone hydrochloride is given concomitantly with other drugs that depress respiration [see Warnings and Precautions (5.2, 5.4)]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.6 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.

5.7 Severe Hypotension

Hydromorphone hydrochloride 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)]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of hydromorphone hydrochloride. In patients with circulatory shock, hydromorphone hydrochloride may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of hydromorphone hydrochloride in patients with circulatory shock.

5.8 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), hydromorphone hydrochloride may reduce respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with hydromorphone hydrochloride.

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

5.9 Risks of Use in Patients with Gastrointestinal Conditions

Hydromorphone hydrochloride is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. Avoid the use of hydromorphone hydrochloride in patients with other GI obstruction.

Because the hydromorphone hydrochloride extended-release tablet is nondeformable and does not appreciably change in shape in the GI tract, hydromorphone hydrochloride is contraindicated in patients with preexisting severe gastrointestinal narrowing (pathologic oriatrogenic, for example: esophageal...
motility disorders, small bowel inflammatory disease, “short gut” syndrome due to adhesions or decreased transit time, past history of peptone fistula, 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 may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

### 5.10 Increased Risk of Seizures in Patients with Seizure Disorders

The hydromorphone in hydromorphone hydrochloride may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during hydromorphone hydrochloride therapy.

### 5.11 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including hydromorphone hydrochloride. 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)].

When discontinuing hydromorphone hydrochloride, gradually taper the dose [see Dosage and Administration (2.4)]. Do not abruptly discontinue hydromorphone hydrochloride [see Drug Abuse and Dependence (9.3)].

### 5.12 Sulfites

Hydromorphone hydrochloride contains 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)].

### 5.13 Risks of Driving and Operating Machinery

Hydromorphone hydrochloride 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 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 (5.3)]
- Interactions with Benzodiazepine or Other CNS Depressants [see Warnings and Precautions (5.4)]
- Adrenal Insufficiency [see Warnings and Precautions (5.6)]
- Seizures [see Warnings and Precautions (5.8)]
- Withdrawal [see Warnings and Precautions (5.11)]

### 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 was administered to a total of 2,524 patients in 15 controlled and uncontrolled clinical studies. Of these, 423 patients were exposed to hydromorphone hydrochloride 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 Titrator Phase | Double-Blind Treatment Phase |
| Hydromorphone | | |
Investigations:
Injury, poisoning and procedural complications:
Infections and infestations:

decreased temperature change, feeling jittery, hangover, gait disturbance, feeling drunk, body temperature

General disorders and administration site conditions:
defecation

Gastrointestinal disorders:
Eye disorders:
Endocrine disorders:
Ear and labyrinth disorders:
Cardiac disorders:

are listed in descending order within each System Organ Class:

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 in 14 Clinical Studies by Preferred Term

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>All Patients (N=2,474)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>765 (31)</td>
</tr>
<tr>
<td>Nausea</td>
<td>684 (28)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>337 (14)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>367 (15)</td>
</tr>
<tr>
<td>Headache</td>
<td>308 (12)</td>
</tr>
<tr>
<td>Asthenia/Fatigue</td>
<td>272 (11)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>262 (11)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>201 (8)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>193 (8)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>161 (7)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>143 (6)</td>
</tr>
<tr>
<td>Edema Peripheral</td>
<td>135 (5)</td>
</tr>
<tr>
<td>Anorexia/Decreased Appetite</td>
<td>139 (6)</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>121 (5)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>115 (5)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>95 (4)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>95 (4)</td>
</tr>
<tr>
<td>Dyspepsia*</td>
<td>88 (4)</td>
</tr>
<tr>
<td>Depression</td>
<td>81 (3)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>76 (3)</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>74 (3)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>72 (3)</td>
</tr>
<tr>
<td>Rash</td>
<td>64 (3)</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>63 (3)</td>
</tr>
<tr>
<td>Pain</td>
<td>58 (2)</td>
</tr>
<tr>
<td>Drug Withdrawal Syndrome</td>
<td>55 (2)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>52 (2)</td>
</tr>
<tr>
<td>Fall</td>
<td>51 (2)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>51 (2)</td>
</tr>
</tbody>
</table>

* 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 less than 2% and are listed in descending order within each System Organ Class:

Cardiac disorders: palpitations, tachycardia, bradycardia, extrasystoles

Ear and labyrinth disorders: vertigo, dizziness

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: corrosion, 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, hypothermia, paresthesia, disturbance in attention, memory impairment, dysharmony, syncope, balance disorder, dysgeusia, depressed level of consciousness, coordination abnormal, hypomnesis, myoclonus, dyskinesia, crying, hyperreflexia, encephalopathy, cognitive disorder, confusion, psychomotor hyperactivity

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

Renal and urinary disorders: dysuria, urinary retention, urinary frequency, urinary hesitancy, 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 serotoninergic 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 (5.6)].

Anaphylaxis: Anaphylactic reaction has been reported with ingredients contained in hydromorphone hydrochloride extended-release tablets [see Contraindications (4) and Warnings and Precautions (5.12)].

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see Clinical Pharmacology (12.2)].

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

<table>
<thead>
<tr>
<th>Drugs Class</th>
<th>Clinical Impact</th>
<th>Intervention</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines and Other Central Nervous System (CNS) Depressants</td>
<td>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.</td>
<td>If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue hydromorphone hydrochloride extended-release tablets if serotonin syndrome is suspected.</td>
<td>Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.</td>
</tr>
<tr>
<td>Serotonergic Drugs</td>
<td>The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.</td>
<td></td>
<td>Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-hydroxytryptamine (5-HT3) receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).</td>
</tr>
<tr>
<td>Monoamine Oxidase Inhibitors (MAOIs)</td>
<td>The use of hydromorphone hydrochloride extended-release tablets is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.</td>
<td></td>
<td>Phenelzine, tranylcypromine, linezolid</td>
</tr>
<tr>
<td>Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics</td>
<td>May reduce the analgesic effect of hydromorphone hydrochloride extended-release tablets and/or precipitate withdrawal symptoms [see Warnings and Precautions (5.11)].</td>
<td></td>
<td>Buprenorphine, naltrexone</td>
</tr>
</tbody>
</table>
Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see Warnings and Precautions (5.3)]. 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 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of 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 (5.3)].

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 is 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 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 breast feeding is not recommended during treatment with hydromorphone hydrochloride. 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 since hydromorphone is excreted in the milk.

Clinical Considerations

Monitor infants exposed to hydromorphone hydrochloride 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

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Adverse Reactions (6.2), Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

The safety and effectiveness of hydromorphone hydrochloride 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. Titrated the dosage of hydromorphone hydrochloride slowly in geriatric patients and monitor closely 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 monitor 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 (Cmax and AUC0-∞) were observed in patients with moderate hepatic impairment (Child-Pugh Group B). Start patients with moderate hepatic impairment on 25% of the hydromorphone hydrochloride dose that would be used in patients with normal hepatic function. Closely monitor patients with moderate hepatic impairment for respiratory and central nervous system depression during initiation of therapy with hydromorphone hydrochloride and during dose titration. The pharmacokinetics of hydromorphone in severe hepatic impairment patients have not been studied. As further increases in Cmax and AUC0-∞ of hydromorphone in this group are expected, use of alternate analgesics is recommended [see Dosage and Administration (2.5)].

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 (Cmax and AUC0-∞) in moderate (CLcr = 40 to 50 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 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 and during dose titration. As hydromorphone hydrochloride-release tablets is 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 (2.6)].

9. DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Hydromorphone hydrochloride contains hydromorphone, a Schedule II controlled substance.

9.2 Abuse

Hydromorphone hydrochloride contains hydromorphone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, oxycodone, methadone, morphine, oxymorphone and tapentadol. Hydromorphone hydrochloride can be abused and is subject to misuse, abuse, addiction, and criminal diversion [see Warnings and Precautions (5.1)].

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

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

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

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

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

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare provider should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true...
Hydromorphone hydrochloride, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

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

Risks Specific to Abuse of Hydromorphone Hydrochloride

Hydromorphone hydrochloride is for oral use only. Abuse of hydromorphone hydrochloride poses a risk of overdose and death. This risk is increased with concurrent abuse of hydromorphone hydrochloride with alcohol and other central nervous system depressants. Taking cut, broken, chewed, or dissolved hydromorphone hydrochloride enhances drug release and increases the risk of overdose and death.

With intravenous abuse, the inactive ingredients in hydromorphone hydrochloride extended-release tablets, especially polyethylene oxide, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, embolism and death, and increased risk of endocarditis and valvular heart injury. 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 chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

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

Hydromorphone hydrochloride should not be abruptly discontinued [see Dosage and Administration (2.3)]. If hydromorphone hydrochloride is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see Warnings and Precautions (5.3)].

10 OVERDOSAGE

Clinical Presentation

Acute overdose with hydromorphone hydrochloride can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

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 techniques.

The opioid antagonists, naloxone and nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to hydromorphone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to hydromorphone overdose.

Because the duration of reversal is expected to be less than the duration of action of hydromorphone in hydromorphone hydrochloride, carefully monitor the patient until spontaneous respiration is reliably reestablished. Hydromorphone hydrochloride 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 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. Hydromorphine 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_{25}NO_{3}·HCl. The compound has the following structural formula:
Hydromorphone hydrochloride extended-release tablets also contain the following inactive ingredients: cellulose acetate, copovidone, hypromellose, iron oxide black, iron oxide red (8 mg and 16 mg only), iron oxide yellow (12 mg and 16 mg only), lactose monohydrate, lecithin (soya) (32 mg only) magnesium stearate, polyethylene glycol, polyvinyl alcohol (8 mg and 16 mg only), propylene glycol, sodium chloride, talc (8 mg, 12 mg, 16 mg, and 32 mg only) 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 is 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 pathognomonic (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 or 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. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date (see Adverse Reactions (6.2)).

Effects on the Immune System

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

Concentration-Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of hydromorphone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance (see Dosage and Administration (2.1, 2.3)).

Concentration-Adverse Reaction Relationships

There is a relationship between increasing hydromorphone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions (see Dosage and Administration (2.1, 2.2, 2.3)).

12.3 Pharmacokinetics
Absorption
Hydromorphone hydrochloride is an extended-release formulation of hydromorphone that produces a gradual increase in hydromorphone concentrations. Following a single-dose administration of hydromorphone hydrochloride, plasma concentrations gradually increase over 6 to 8 hours, and thereafter concentrations are sustained for approximately 18 to 24 hours post-dose. The median $T_{\text{max}}$ 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 over the dose range 8 to 64 mg, with a dose-proportional increase in $C_{\text{max}}$ and overall exposure (AUC$_{0-\infty}$) (see Table 4). 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. At steady state, hydromorphone hydrochloride 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 once daily and immediate-release hydromorphone four times daily in adults is comparable, as presented in Table 4.

Table 5. Mean (±SD) Hydromorphone Hydrochloride Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage</th>
<th>$T_{\text{max}}$ (hrs)</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>AUC (ng·hr/mL)</th>
<th>$T_{\frac{1}{2}}$ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Dose (N = 31)</td>
<td>8 mg</td>
<td>12 (4-30)</td>
<td>0.93 (1.01)</td>
<td>18.1 (5.8)</td>
<td>10.6 (4.3)</td>
</tr>
<tr>
<td></td>
<td>16 mg</td>
<td>16 (6-30)</td>
<td>1.69 (0.78)</td>
<td>36.5 (11.3)</td>
<td>10.3 (2.4)</td>
</tr>
<tr>
<td></td>
<td>32 mg</td>
<td>16 (4-24)</td>
<td>3.25 (1.37)</td>
<td>72.2 (24.3)</td>
<td>11.0 (3.2)</td>
</tr>
<tr>
<td></td>
<td>64 mg</td>
<td>16 (6-30)</td>
<td>6.61 (1.75)</td>
<td>156.0 (30.6)</td>
<td>10.9 (3.8)</td>
</tr>
<tr>
<td>Multiple Dose† (N = 29)</td>
<td>16 mg q24h</td>
<td>12 (6-24)</td>
<td>3.54 (0.96)$\dagger$</td>
<td>57.6 (16.3)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>IR 4 mg q6h</td>
<td>0.75 (0.5-2)</td>
<td>5.28 (1.37)$\S\S$</td>
<td>54.8 (14.8)</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = not applicable
* Median (range) reported for $T_{\text{max}}$
† Steady-state results on Day 5 (0-24 hours)
‡ $C_{\text{max}}$ 2.15 (0.87) ng/mL
§ $C_{\text{max}}$ 1.47 (0.42) ng/mL
Food Effect
The pharmacokinetics of hydromorphone hydrochloride are not affected by food as indicated by bioequivalence when administered under fed and fasting conditions. Therefore, hydromorphone hydrochloride may be administered without regard to meals. When a 16 mg dose of hydromorphone hydrochloride was administered to healthy volunteers immediately following a high-fat meal, the median time to $C_{\text{max}}$ ($T_{\text{max}}$) 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 protein 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 Cmax 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 (Cmax and AUC0-∞) 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 Cmax and AUC0-∞ of hydromorphone in this group is expected. Start patients with moderate hepatic impairment on 25% of the usual dose of hydromorphone hydrochloride 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 (2.5) 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 (Cmax and AUC0-∞) 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 dose for patients with normal renal function and closely monitor for respiratory and central nervous system depression during dose titration. As hydromorphone hydrochloride is 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 (2.6) 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 in healthy, fasted or fed volunteers. The results showed that the hydromorphone mean AUC0-∞ 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 AUC0-∞ was similarly unaffected in subjects following the co-administration of hydromorphone hydrochloride and alcohol (240 mL of 20% or 4% alcohol).

The change in geometric mean Cmax with concomitant administration of alcohol and hydromorphone hydrochloride ranged from an increase of 10% to 31% across all conditions studied. The change in mean Cmax was greater in the fasted group of subjects. Following concomitant administration of 240 mL of 40% alcohol while fasting, the mean Cmax 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 Cmax 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 Cmax increased by 19% on average and as much as 73% for an individual subject. The range of median Tmax 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 on 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. 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.

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 was investigated in a double-blind, placebo-controlled, randomized withdrawal study in opioid tolerant patients with moderate-to-severe low back pain. Patients were considered opioid tolerant if they were currently on opioid therapy that was greater than or equal to 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, 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 during the open-label conversion and titration phase.

During the double-blind treatment phase, patients randomized to hydromorphone hydrochloride 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 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 and 33% of patients treated with placebo completed the 12-week treatment period.

Hydromorphone hydrochloride 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Hydromorphone hydrochloride Extended-Release Tablet Strengths

<table>
<thead>
<tr>
<th>Strength</th>
<th>Color</th>
<th>Tablets Description</th>
<th>Bottle Count</th>
<th>NDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 mg</td>
<td>Reddish brown</td>
<td>Round, film-coated tablets with black imprint stating WPI and 3629 on one side and plain on the other side</td>
<td>30</td>
<td>0591-3629-30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0591-3629-01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0591-3629-10</td>
</tr>
<tr>
<td>12 mg</td>
<td>Dark yellow</td>
<td>Round, film-coated tablets with black imprint stating WPI and 3739 on one side and plain on the other side</td>
<td>30</td>
<td>0591-3739-30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0591-3739-01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0591-3739-10</td>
</tr>
<tr>
<td>16 mg</td>
<td>Beige to light yellow</td>
<td>Round, film-coated tablets with black imprint stating WPI and 3630 on one side and plain on the other side</td>
<td>30</td>
<td>0591-3630-30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0591-3630-01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0591-3630-10</td>
</tr>
<tr>
<td>32 mg</td>
<td>White to off-white</td>
<td>Round, film-coated tablets with black imprint stating WPI and 3631 on one side and plain on the other side</td>
<td>30</td>
<td>0591-3631-30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>0591-3631-01</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0591-3631-10</td>
</tr>
</tbody>
</table>

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

17 PATIENT COUNSELING INFORMATION

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

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 doses [see Warnings and Precautions (5.2)]. Advise...
inform patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

**Accidental Ingestion**
Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [see Warnings and Precautions (5.2)]. Instruct patients to take steps to store hydromorphone hydrochloride extended-release tablets securely and to dispose of unused hydromorphone hydrochloride extended-release tablets by flushing the tablets down the toilet.

**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 (5.4), Drug Interactions (7)].

**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].

**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 (5.6)].

**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)
- Do not discontinue hydromorphone hydrochloride extended-release tablets without first discussing the need for a tapering regimen with the prescriber [see Dosage and Administration (2.4)].

**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 (5.12), and Adverse Reactions (6.2)].

**Pregnancy**

**Neonatal Opioid Withdrawal Syndrome**
Inform female patients of reproductive potential that 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 [see Warnings and Precautions (5.3), 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 chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [Use In Specific Populations (8.3)].

**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 (5.13)].
Hydromorphone Hydrochloride Extended-Release Tablets

Medication Guide

**Hydromorphone Hydrochloride Extended-Release Tablets**: This is a prescription medicine. Do not take it if you are allergic to any ingredient in this medicine.

**Important Information**

- **Emergency Help**: If you take too many hydromorphone hydrochloride extended-release tablets (overdose), call emergency help right away or go to the nearest emergency room.
- **Children and Safety**: Store hydromorphone hydrochloride extended-release tablets in a place to prevent stealing or abuse. Selling or giving away hydromorphone extended-release tablets is illegal.

**Before Taking Hydromorphone Hydrochloride Extended-Release Tablets**

Before you take hydromorphone hydrochloride extended-release tablets, tell your healthcare provider if you have any of these conditions:

- Head injury, seizures, liver, kidney, thyroid problems
- Problems urinating, pancreas or gallbladder problems
- Abuse of street or prescription drugs, alcohol addiction, or mental health problems

**Tell Your Healthcare Provider**

- **Pregnancy**: If you are or plan to become pregnant. Hydromorphone hydrochloride extended-release tablets can cause withdrawal symptoms in your newborn baby if you use this medicine during pregnancy.
- **Breastfeeding**: If you are breastfeeding. Hydromorphone hydrochloride extended-release tablets can pass into your breast milk.

**When Taking Hydromorphone Hydrochloride Extended-Release Tablets**

- Do not take this medicine if you are allergic to any ingredient in this medicine.
- 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.

**While Taking Hydromorphone Hydrochloride Extended-Release Tablets**

- Do not take with any other opioid drugs, other prescription or over-the-counter medicine, or street drugs.
- Do not stop taking without talking to your healthcare provider.

**The Possible Side Effects**

- Nausea, vomiting, diarrhea, constipation, unusual tiredness, weakness, muscle pain, high blood pressure, fast heartbeat, feeling light-headed, dizziness, confusion, hallucinations, or trouble breathing. Call your healthcare provider if you have any of these symptoms and they are severe.
Get emergency medical help if you have:
- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme
drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking,
stiff muscles, or mental changes such as confusion.

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

Manufactured by:
Actavis Laboratories FL, Inc.
Fort Lauderdale, FL 33314 USA

Distributed by:
Actavis Pharma, Inc.
Parsippany, NJ 07054 USA

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

Revised: February 2017

PRINCIPAL DISPLAY PANEL
NDC 0591-3629-30
Hydromorphone
Hydrochloride
Extended-Release Tablets
Once daily
8 mg
30 tablets
Rx Only

PRINCIPAL DISPLAY PANEL
NDC 0591-3739-30
Hydromorphone
Hydrochloride
Extended-Release Tablets
Once daily
12 mg
30 tablets
Rx Only

PRINCIPAL DISPLAY PANEL
NDC 0591-3630-30
Hydromorphone
Hydrochloride
Extended-Release Tablets
Once daily
16 mg
30 tablets
Rx Only
HYDROMORPHONE HYDROCHLORIDE
hydromorphone hydrochloride tablet, film coated, extended release

Product Information
Product Type: HUMAN PRESCRIPTION DRUG
Route of Administration: ORAL

Active Ingredient/Active Moiety
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<th>Ingredient Name</th>
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Inactive Ingredients
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<td>COPovidone K25-31 (UNII: D9C330MD8B)</td>
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</tr>
<tr>
<td>HYPERMELLOSES (UNII: 3WX629V1W0)</td>
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</tr>
<tr>
<td>POLYVINYLS ALCOHOL, UNSPECIFIED (UNII: 52BS50Y990)</td>
<td></td>
</tr>
<tr>
<td>PROPYLENE GLYCOL (UNII: 66Q0Q167V3)</td>
<td></td>
</tr>
<tr>
<td>SODIUM CHLORIDE (UNII: 4Q569Q96X)</td>
<td></td>
</tr>
<tr>
<td>TITANIUM DIOXIDE (UNII: 15F962V21P)</td>
<td></td>
</tr>
</tbody>
</table>

Product Characteristics
Color: BROWN (reddish brown)
Score: no score
Shape: ROUND
Size: 10mm

Packaging
- #1 NDC: 0591-3629-01, 100 in 1 BOTTLE, Type 0: Not a Combination Product
- #1 NDC: 0591-3629-10, 1000 in 1 BOTTLE, Type 0: Not a Combination Product
- #1 NDC: 0591-3629-30, 30 in 1 BOTTLE, Type 0: Not a Combination Product

Marketing Information
Marketing Category: ANDA
Application Number or Monograph Citation: ANDA202144
Marketing Start Date: 05/21/2014
Marketing End Date: 02/29/2020

HYDROMORPHONE HYDROCHLORIDE
hydromorphone hydrochloride tablet, film coated, extended release

Product Information
Product Type: HUMAN PRESCRIPTION DRUG
Route of Administration: ORAL

Active Ingredient/Active Moiety
<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYDROMORPHONE HYDROCHLORIDE (UNII: L960UP2KRW)</td>
<td>HYDROMORPHONE - UNII:Q812464R06</td>
<td>12 mg</td>
</tr>
</tbody>
</table>
## Inactive Ingredients

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>CELLULOSE ACETATE (UNII: 382P97GVB6)</td>
<td></td>
</tr>
<tr>
<td>COPovidone K25-31 (UNII: D9G330M1DB)</td>
<td></td>
</tr>
<tr>
<td>HYDROMELLOSES (UNII: 393x029V3W)</td>
<td></td>
</tr>
<tr>
<td>FERROSOFERRIC OXIDE (UNII: XM80B7FS37)</td>
<td></td>
</tr>
<tr>
<td>FERRIC OXIDE YELLOW (UNII: EX438O2MRT)</td>
<td></td>
</tr>
<tr>
<td>LACTOSE MONOHYDRATE (UNII: 5QG2Q8CH6X)</td>
<td></td>
</tr>
<tr>
<td>MAGNESIUM STEARATE (UNII: 78997MD110)</td>
<td></td>
</tr>
<tr>
<td>POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)</td>
<td></td>
</tr>
<tr>
<td>PROPYLENE GLYCOL (UNII: 6DC9Q167V3)</td>
<td></td>
</tr>
<tr>
<td>TITANIUM DIOXIDE (UNII: 15FX39V23P)</td>
<td></td>
</tr>
</tbody>
</table>

## Product Characteristics

<table>
<thead>
<tr>
<th>Color</th>
<th>YELLOW (Beige to light yellow)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>no score</td>
</tr>
<tr>
<td>Shape</td>
<td>ROUND</td>
</tr>
<tr>
<td>Size</td>
<td>10mm</td>
</tr>
<tr>
<td>Flavor</td>
<td></td>
</tr>
<tr>
<td>Imprint Code</td>
<td>WPI3630</td>
</tr>
</tbody>
</table>

## Packaging

<table>
<thead>
<tr>
<th>#</th>
<th>Item Code</th>
<th>Package Description</th>
<th>Marketing Start Date</th>
<th>Marketing End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NDC:0591-3739-01</td>
<td>100 in 1 BOTTLE; Type 0: Not a Combination Product</td>
<td>05/21/2014</td>
<td>03/31/2019</td>
</tr>
<tr>
<td>2</td>
<td>NDC:0591-3739-10</td>
<td>1000 in 1 BOTTLE; Type 0: Not a Combination Product</td>
<td>05/21/2014</td>
<td>05/21/2014</td>
</tr>
<tr>
<td>3</td>
<td>NDC:0591-3739-30</td>
<td>30 in 1 BOTTLE; Type 0: Not a Combination Product</td>
<td>05/21/2014</td>
<td>05/21/2014</td>
</tr>
</tbody>
</table>

## Marketing Information

<table>
<thead>
<tr>
<th>Marketing Category</th>
<th>Application Number or Monograph Citation</th>
<th>NDC:0591-3630</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDA</td>
<td>ANDA20244</td>
<td></td>
</tr>
</tbody>
</table>

## Active Ingredient/Active Moiety

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYDROMORPHONE HYDROCHLORIDE (UNII: L960UP2KRW) (HYDROMORPHONE - HYDROMORPHONE HYDROCHLORIDE)</td>
<td>16 mg</td>
<td></td>
</tr>
<tr>
<td>NDC:0591363030</td>
<td>30 in 1 BOTTLE; Type 0: Not a Combination Product</td>
<td>05/21/2014</td>
</tr>
<tr>
<td>NDC:0591363030</td>
<td>30 in 1 BOTTLE; Type 0: Not a Combination Product</td>
<td>05/21/2014</td>
</tr>
</tbody>
</table>

| Marketing Information |
| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
| ANDA | ANDA20244 | 05/21/2014 | 05/31/2019 |

**Labeler - Actavis Pharma, Inc. (19723554)**

Revised: 2/2017 Actavis Pharma, Inc.